A New Highly Selective and Easily Displaced Chiral Auxiliary for Aldol Reactions

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A mis padres, Tino y Adela,
y a Javi.

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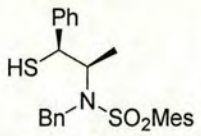
ABSTRACT

An efficient route for the synthesis of a new highly selective and easily displaced chiral auxiliary **117** for the asymmetric boron-mediated aldol reaction has been developed in 5 steps from norephedrine.



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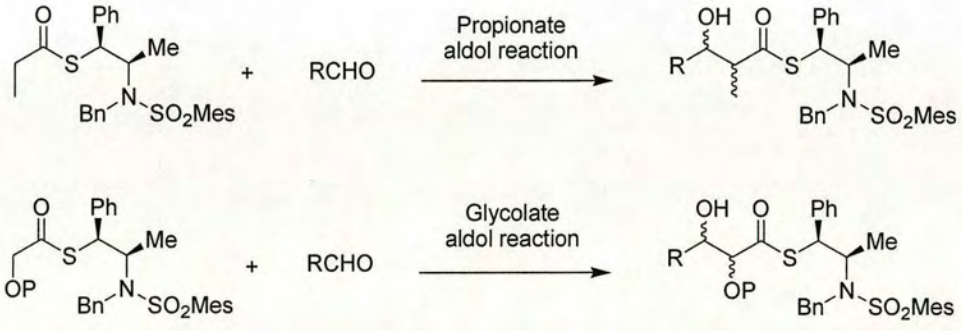
This novel chiral auxiliary has been shown to mediate *anti* and *syn* propionate and glycolate aldol reactions with a range of aldehydes in excellent yield (60-98%) and with good to excellent diastereoselectivity. Details of the methods which have been used to assign the absolute and relative stereochemistry of the aldol adducts are also summarised.



P = Me, Bn, TBDPS

The facile displacement of auxiliary **117** with a range of nucleophiles under very mild conditions to give the corresponding phosphonate esters, alcohols, acids, SNAc thiolesters and methyl esters has been demonstrated.

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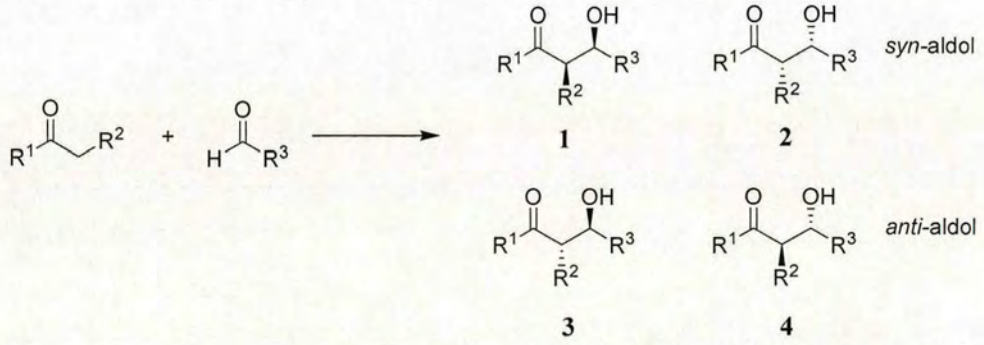
[92]Fanjul, S.; Hulme, A. N.; White, J. W. *Org. Lett.* **2006**, *8*, 4219-4222.

CHAPTER 1: INTRODUCTION

1.1 ASYMMETRIC BORON-MEDIATED ALDOL REACTIONS

The powerful aldol reaction involves the reaction of an enol or an enolate and an aldehyde or a ketone to form a new carbon-carbon bond. Intense and extensive studies on the reaction have covered a wide variety of reaction conditions and structural modifications for the development of efficient procedures, leading to high levels of stereoselection.[1,2]

In this regard, the use of chiral boron enolate reagents is notably successful and can give rise to the formation of the new carbon-carbon bond in a regio-, diastereo- and enantioselective manner. Up to two new stereocentres are created from two prochiral carbon atoms, producing four possible stereoisomers **1-4** (**scheme 1**).

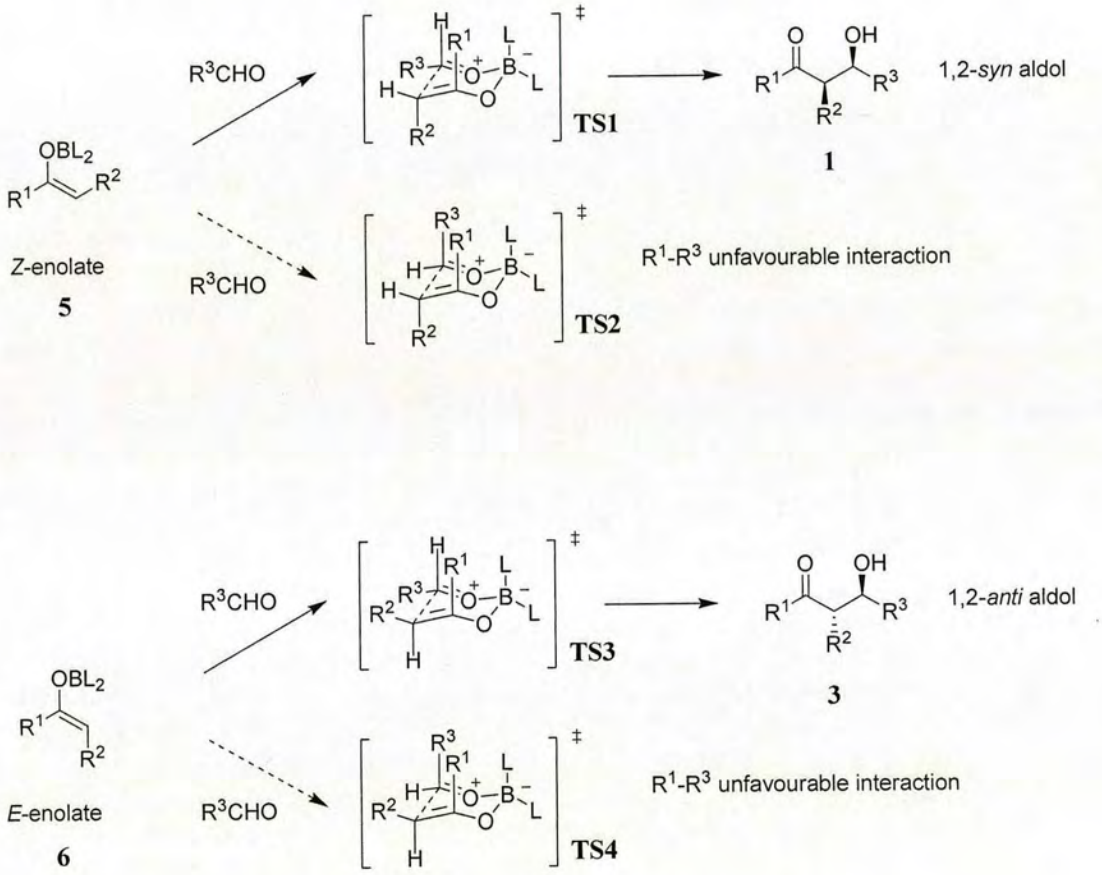


Scheme 1: Four possible stereoisomers of the aldol reaction.

1.1.1 Relative Stereocontrol

The *Z:E* geometry of the enol borinate[3,4] intermediate formed in the presence of a tertiary amine base determines the relative stereochemistry of the kinetically controlled boron aldol reaction.

Boron-mediated aldol reactions are considered to go through a highly ordered cyclic transition state known as the Zimmerman-Traxler[5] transition state. In the favoured transition states, the aldehyde substituent (R^3) adopts a more stable equatorial position, avoiding unfavourable 1,3-diaxial interactions.

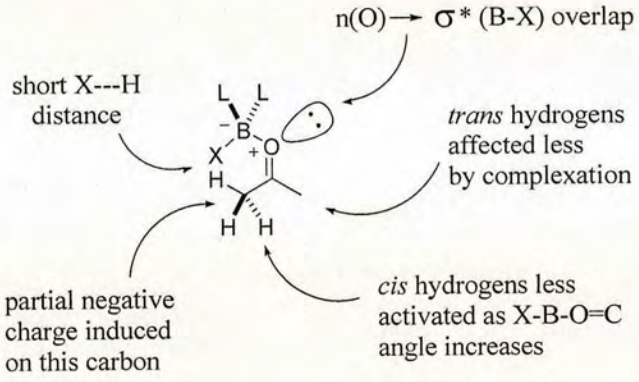


Scheme 2: Zimmerman-Traxler[5] transition states for *Z*- and *E*-enolates.

It can be seen from **scheme 2** that the enolate geometry directly affects the stereochemistry of the products; (*Z*)-boron enolates give *syn* products, and (*E*)-boron enolates give *anti* products.[3,4] Therefore, the ability to selectively obtain either enolate is of crucial importance.

L_2BX reagents with a variety of ligands and leaving groups[6-9] have been investigated to generate either *E* or *Z* enolates for a number of different substrates. Brown[10,11] has studied the effects of varying the leaving groups of boron reagents with respect to stereochemical control of aldol adducts. The combination of small ligands on boron (*e.g.* *n*-butyl), a good leaving group (*e.g.* triflate) and a bulky amine base (*e.g.* diisopropylethylamine) usually leads to *Z*-selective enolisation. However, the use of bulky ligands on boron (*e.g.* cyclohexyl), a poor leaving group (*e.g.* chloride) and a small amine base (*e.g.* triethylamine) usually promotes *E*-enolate formation.[10-12]

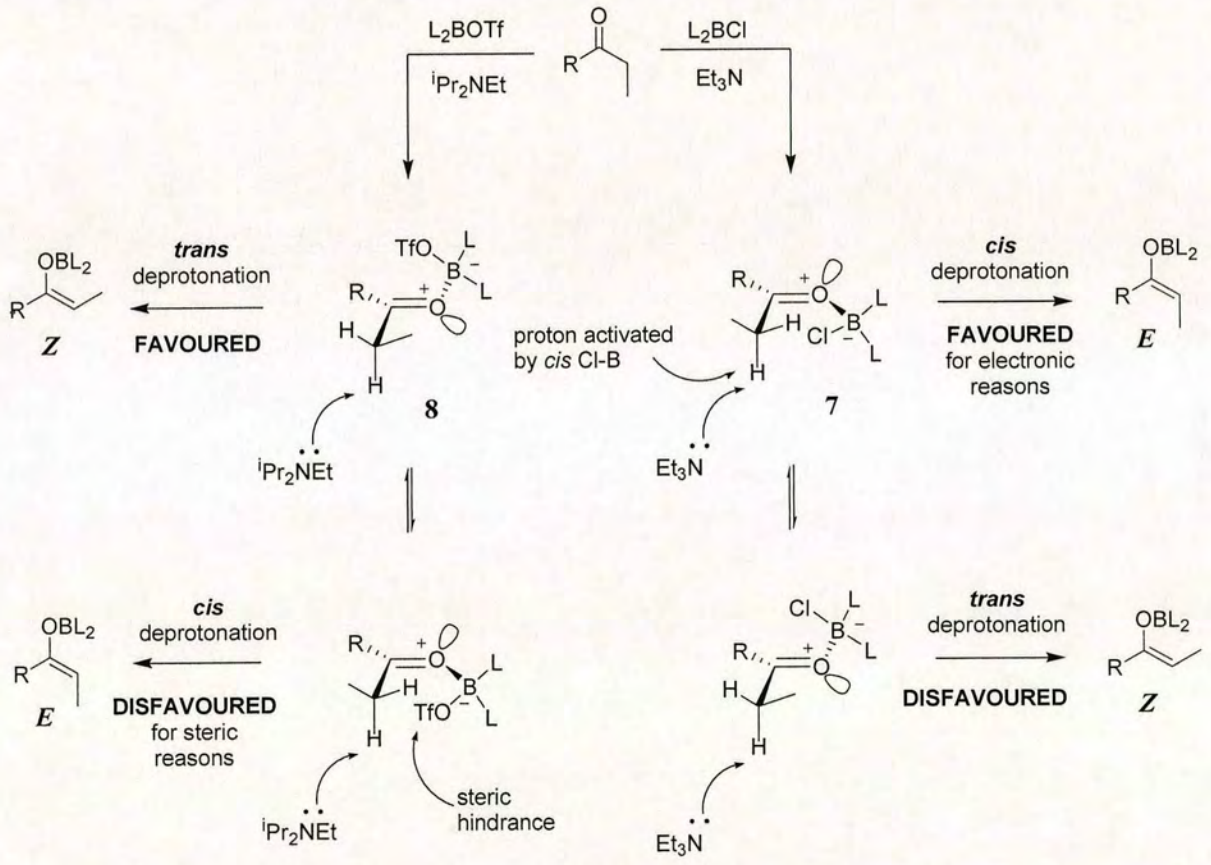
Two hypotheses have been postulated to explain the stereochemical selectivity of the enolate formation. Molecular orbital calculations by Goodman and Paterson on $R^1R^2CO{\bullet}BH_2X$ complexes (X = F, Cl) (used as a model for $R^1R^2CO{\bullet}BL_2X$ complexes), have shown that an anomeric effect between the uncomplexed lone pair on the carbonyl and the B-X antibonding orbital (σ^*) exists, causing the B-X bond to eclipse the C=O bond (**scheme 3**).[13]



Scheme 3: The effect of L_2BX complexation on acetone.[13]

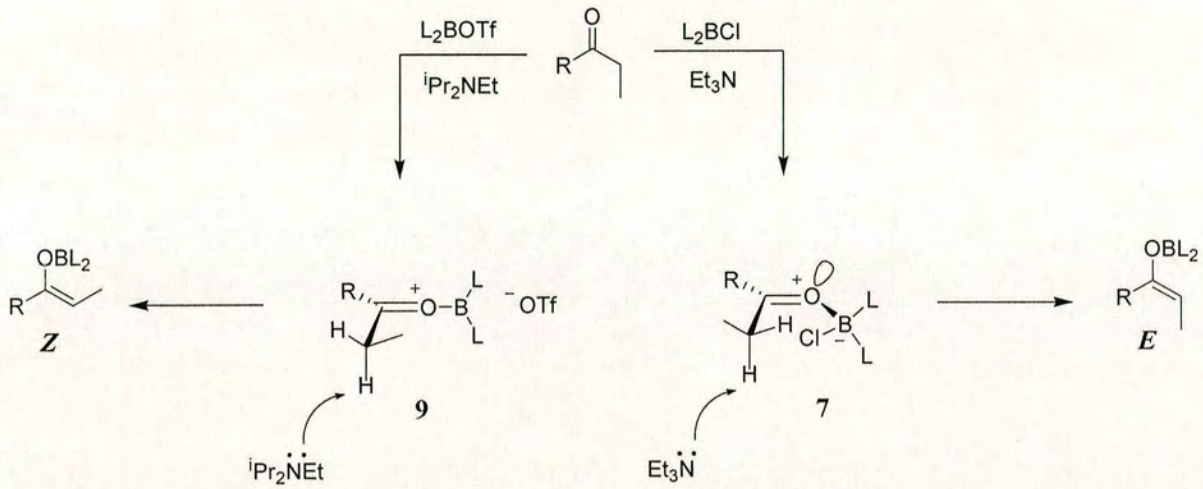
As shown in this acetone-boron complexed model (**scheme 3**) the halogen atom is directed towards one of the hydrogens on the *cis* alkyl group, inducing a partial negative charge on this α-carbon, thereby, activating the *cis* over the *trans* side for enolisation by an unhindered base such as Et_3N via **7** (**scheme 4**).

As the X-B-O=C dihedral angle increases, induced by sterically hindered triflate ligands, the electronic influence on the *cis* alkyl group decreases, and *trans* deprotonation is favoured by a bulky base such as $^iPr_2NEt$ via **8** (**scheme 4**).



Scheme 4: Paterson/Goodman model for deprotonation selectivity.[13]

Corey[9] has proposed an alternative explanation in which the superior leaving group ability of the triflate allows the formation of a linear intermediate **9**, as shown in **scheme 5**.

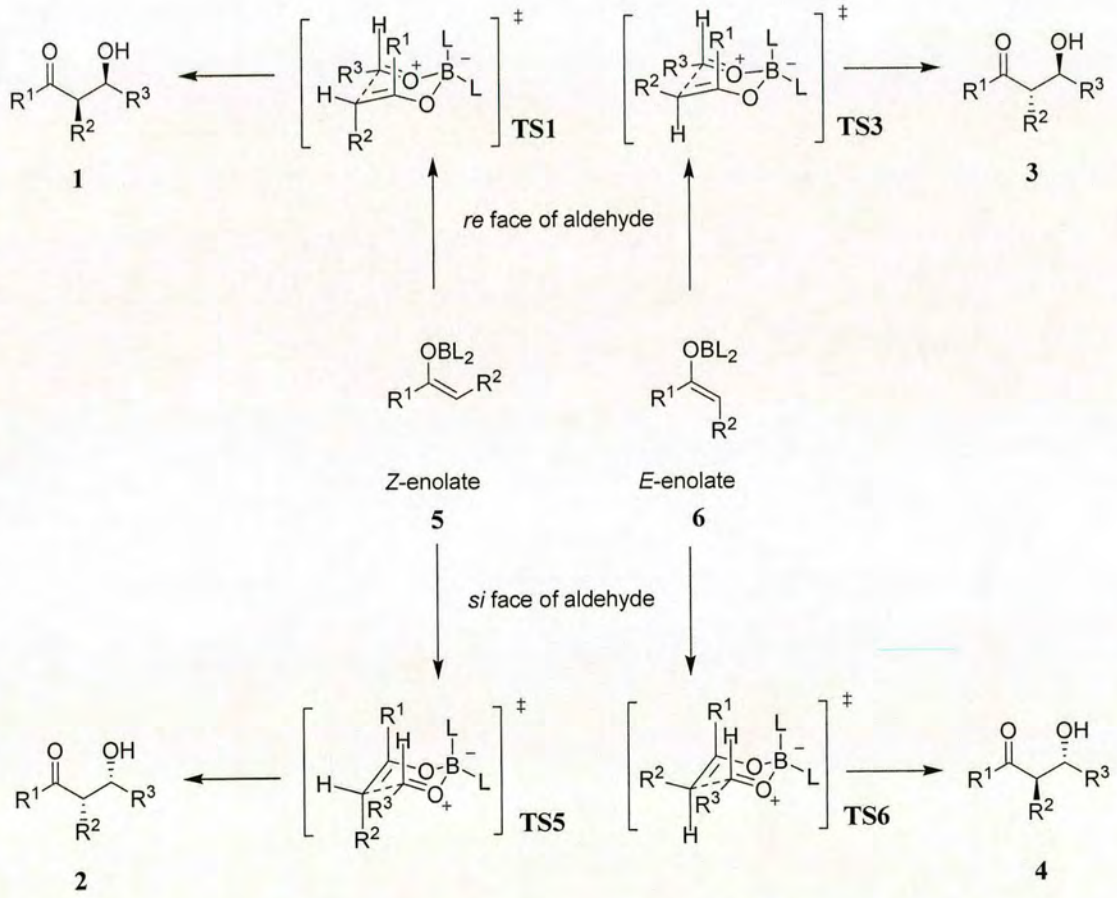


Scheme 5: Corey's model for deprotonation selectivity.[9]

In this hypothesis a good leaving group allows deprotonation to give the *Z*-enolate via **9**, where the methyl group is able to eclipse the C=O-BL_2 bond. In contrast, a poorer leaving group ensures that the bent complex **7** predominates, and deprotonation to give the *E*-enolate takes place preferentially.

1.1.2 Absolute Stereocontrol

To obtain absolute stereocontrol in a boron mediated aldol reaction the enolate must show a high level of π-facial selectivity.[3,4] One of the π-faces of the enolate (**scheme 6**) must therefore be selective for either the *si* or *re* faces of the aldehyde, the *E*-enolate giving the *anti* isomers and the *Z*-enolate giving the *syn* isomers.



Scheme 6: Enantiofacial selectivity in boron aldol reactions.[3,4]

Chiral aldehydes, enolates, boron reagents, and auxiliaries attached to an enolate which can be easily removed, are commonly used on their own or combined, to achieve π-facial selectivity. The use of chiral auxiliaries, which is central to this research, is described below in more detail.

1.1.3 The Use of Chiral Auxiliaries to Obtain Absolute Stereocontrol

Although asymmetric catalysis and biocatalytic methods increasingly allow for the efficient synthesis of many enantiomerically pure compounds,[14-18] chiral auxiliaries remain as one of the principal means through which the aldol reaction finds its application in synthesis.[19-21] A wide range of auxiliaries have been developed, although, two auxiliaries have predominance in the field: the Evans' oxazolidinone **10** (**figure 1**) for *syn* aldol reactions,[22-29] and the Abiko-Masamune auxiliary **11** for *anti* aldol reactions.[30-34]

10 **11**

Figure 1: Evans' and Masamune's auxiliaries.

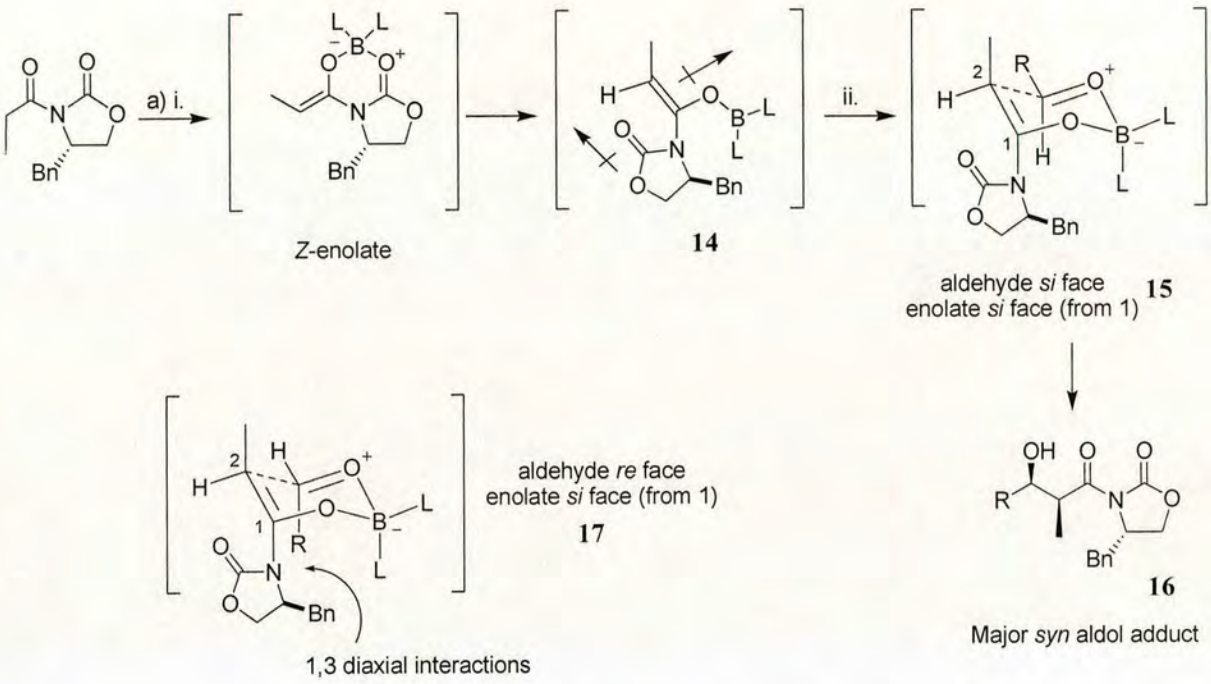
The boron enolate chemistry pioneered by Evans utilising chiral *N*-acyloxazolidin-2-ones derived from α-amino acids has become one of the most popular methods of generating aldol adducts because of the exceptionally high levels of diastereoselection that are possible.[35-37] The original work by Evans involved the pair of chiral oxazolidin-2-one auxiliaries **12** and **13** derived from commercially available *S*-valinol and (1*S*,2*R*)-norephedrine respectively (**figure 2**).

12 **13**

Figure 2: Evans' auxiliaries.

These oxazolidin-2-ones can be conveniently acylated to give a variety of useful chiral acyl equivalents, which undergo highly stereoselective enolisation to form almost exclusively *Z*-enolates, after reacting with a boron triflate and a base (**scheme 7**).

The corresponding *Z*-boron enolates, when reacted with achiral aldehydes, provide aldol adducts in which the α,β-*syn* diastereoisomers are virtually the sole products. The absolute configuration of the two new chiral centres is controlled precisely by the chirality of the chiral auxiliary (**scheme 7**).



Scheme 7: The Evans auxiliary absolute stereocontrol. Typical reagents and conditions: a) i. Bu_2BOTf, Et_3N, CH_2Cl_2, -78 °C; ii. RCHO, -78 °C to 0 °C.

In the above example (**scheme 7**) we have seen that a chiral enolate is able to control the stereochemistry of the newly formed chiral centres in the aldol reaction. It is able to do this by discriminating between each face of the aldehyde it attacks.

If we analyse the transition state **15** which leads to aldol adduct **16** (**scheme 7**), we can see that the *si* face of the aldehyde and the *si* face of the enolate react to give the *syn* aldol adduct **16**. We can also see from transition state **17** that the *si* face of the enolate prefers not to attack the *re* face of the aldehyde, due to unfavourable 1,3-diaxial interactions between the auxiliary and the R group on the aldehyde. Attack from the *re* face of the enolate to either face of the aldehyde is also disfavoured, due to steric crowding over the *re* face as a result of the substituent at the 4-position of the oxazolidin-2-one auxiliary.

This high selectivity makes *N*-acyl oxazolidin-2-ones boron enolates extremely useful in asymmetric synthesis. The *syn*-selective aldol reaction using the Evans methodology has become the most reliable method for the direct synthesis of *syn* β-hydroxycarbonyl systems, with many applications to natural product synthesis reported in recent years.[38-42]

Rizzacasa's formal total synthesis of (+)-zaragozic acid C (**scheme 8**),[39] a potent inhibitor of squalene synthase and farnesyl protein transferase, includes a highly selective Evans-controlled boron aldol reaction.

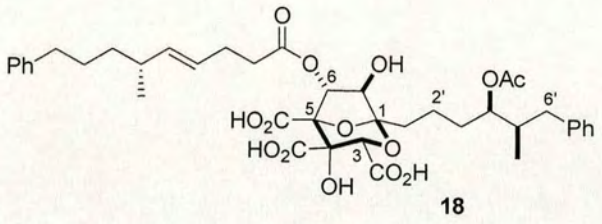


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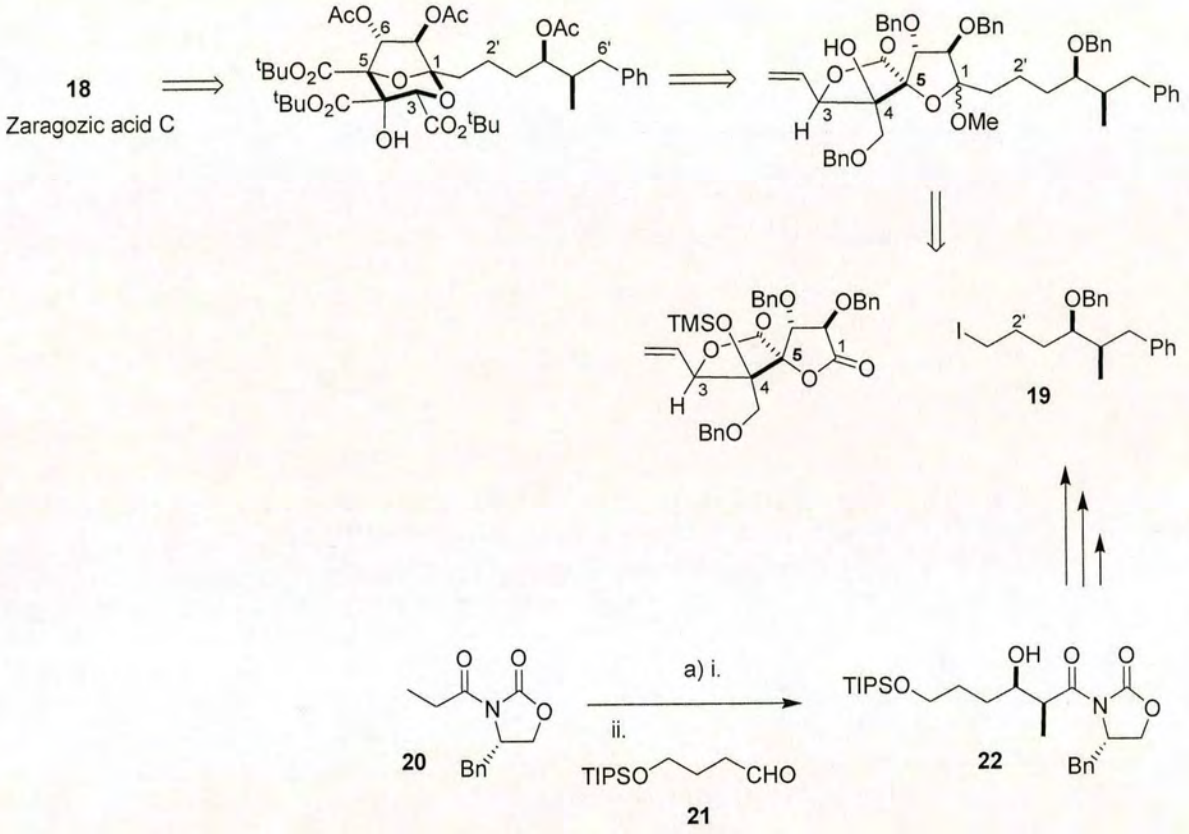
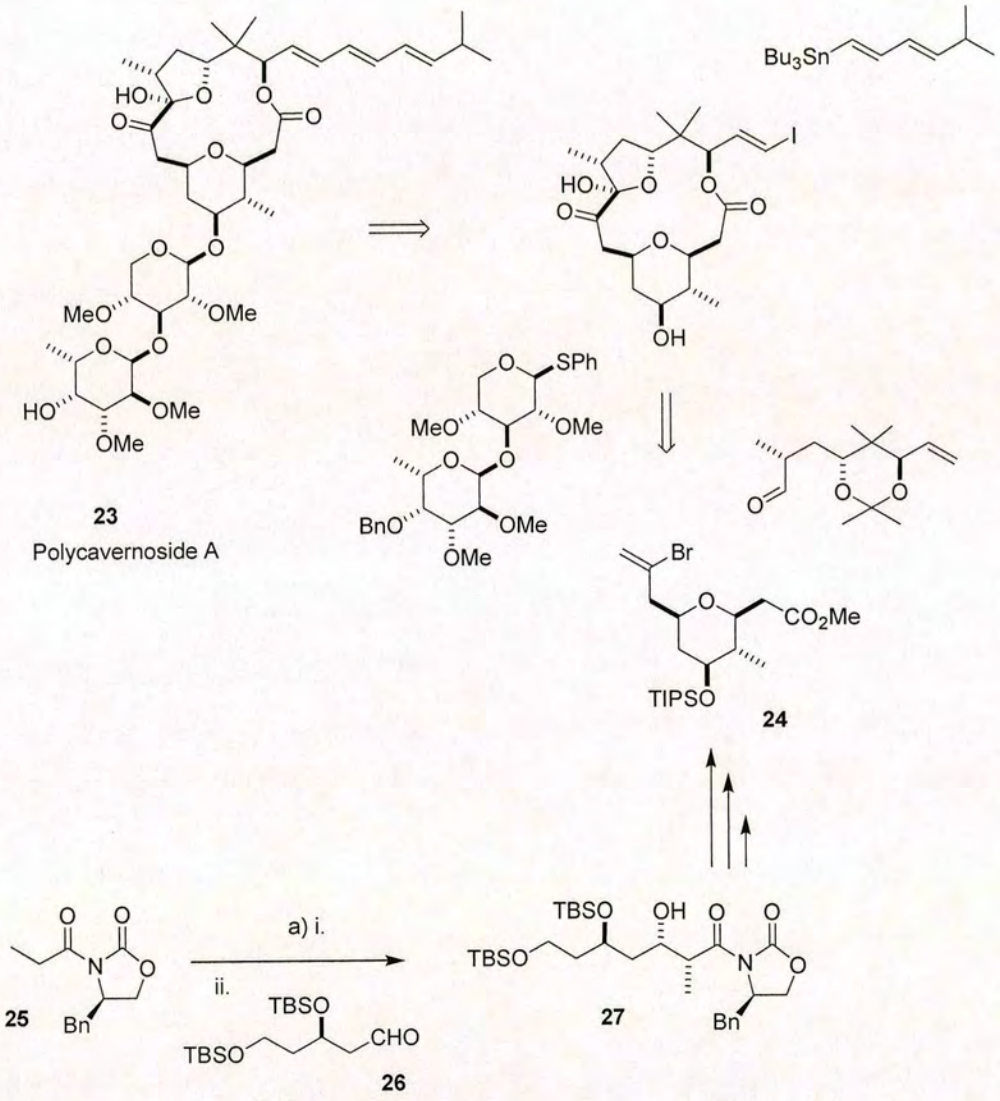
Figure 3: (+)-Zaragozic acid C.

The Evans aldol reaction between the boron enolate derived from oxazolidinone **20** and aldehyde **21** proceeded in excellent yield (90%) and stereoselectivity (>97:3) to afford aldol adduct **22**, a precursor to key fragment **19** in the synthesis of (+)-zaragozic acid C by Rizzacasa (**scheme 8**).[39]



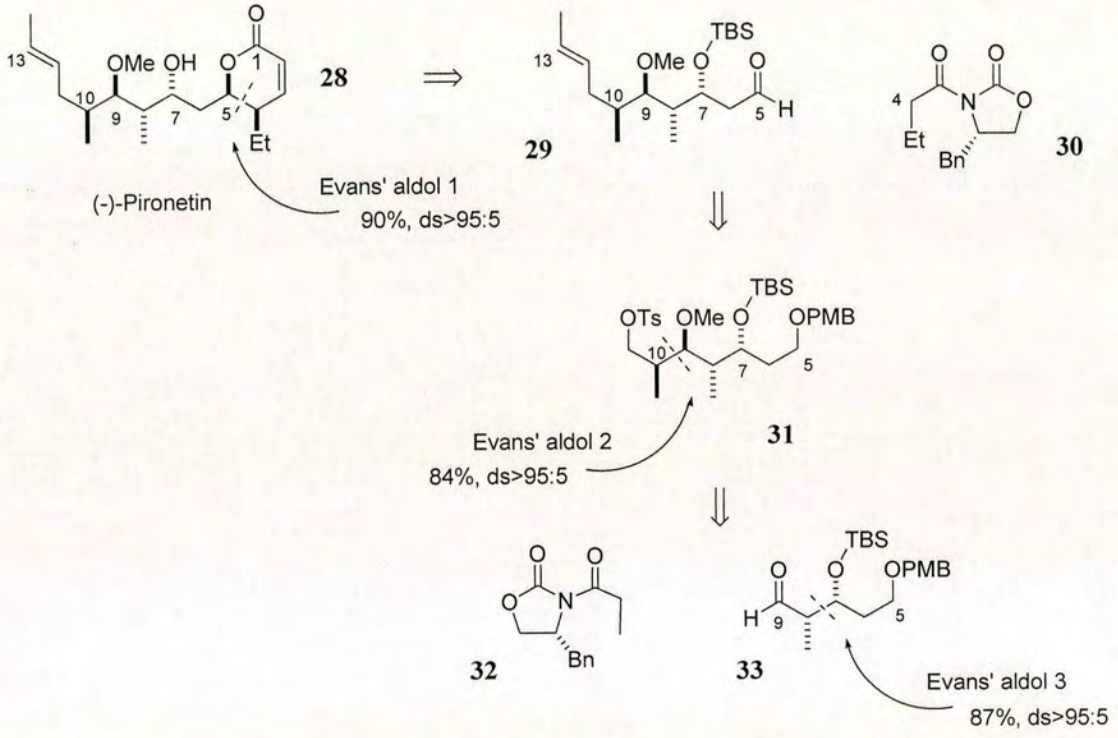
Scheme 8: Retrosynthetic analysis of (+)-zaragozic acid C and Evans aldol reaction towards the synthesis of key fragment **19**. Reagents and conditions: a) i. Bu_2BOTf, $^iPr_2EtN$, -78 °C, CH_2Cl_2; ii. **21**, -78 °C to 0 °C (90%, ds >97:3).

In White's total synthesis of polycavernoside A **23**, a lethal toxin of the red algae *Polycavernosa tsudai*, a *syn*-selective boron-mediated aldol reaction was used to build fragment **24** (**scheme 9**).[41] Evans' methodology was used to generate the boron enolate derived from oxazolidinone **25**. After addition of aldehyde **26**, aldol adduct **27** was recovered in excellent yield (88%) and diastereoselectivity (>94:6) (**scheme 9**).[41]



Scheme 9: Retrosynthetic analysis of Polycavernoside A and Evans aldol reaction towards the synthesis of key fragment **24**. Reagents and conditions: a) i. Bu_2BOTf, Et_3N, -78 °C, CH_2Cl_2; ii. **26**, -78 °C to 0 °C (88%, ds >94:6).

Dias[42] approach to the asymmetric total synthesis of (-)-pironetin **28**, a compound that shows plant growth regulatory activity and immunosuppression as well as a remarkable antitumoral activity, involves the use of three very efficient Evans' oxazolidinone-mediated *syn* aldol reactions (**scheme 10**).



Scheme 10: Retrosynthesis of (-)-pironetin.[42]

As shown in **scheme 10** these three high-yielding Evans' *syn* aldol reactions proceeded in high diastereoselectivities (>95:5) to set up six stereogenic centres in a very efficient manner.

Thus, the asymmetric total synthesis of (-)-pironetin,[42] polycavernoside A,[41] and (+)-zaragozic acid C,[39] can be shown as perfect examples of the high levels of diastereoselectivities that can be attained in oxazolidin-2-one-controlled aldol reactions.

1.2 THE MASAMUNE AUXILIARY

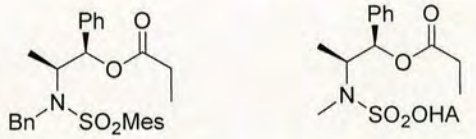
1.2.1 Propionate Aldol Reactions

Numerous efforts have been devoted to the development of efficient procedures for the construction of β-hydroxycarbonyl compounds in a stereodefined fashion. In many cases these methods provide aldol products with high enantioselectivities but appear to present problems in terms of the availability of reagents, the generality of reactions, or the conditions required for reactions.

Studies by Abiko and Masamune[30-34] have shown that the Masamune chiral auxiliary (**figure 4**) can be used to achieve high stereoselectivities in the construction of *anti* and *syn* β-hydroxycarbonyl systems.

Mes = 2,4,6-trimethylphenyl.

OHA = 1,2,3,4,6,7,8,9-octahydroanthracenyl.

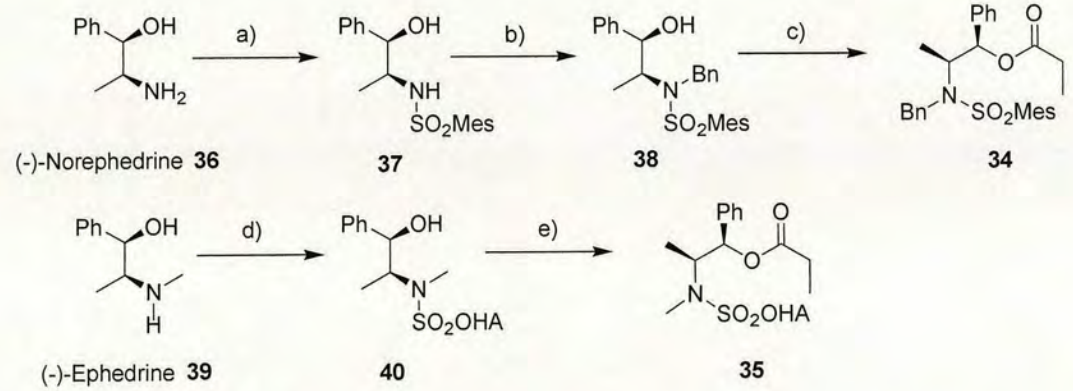


34 **35**

anti-aldol reagent *syn*-aldol reagent

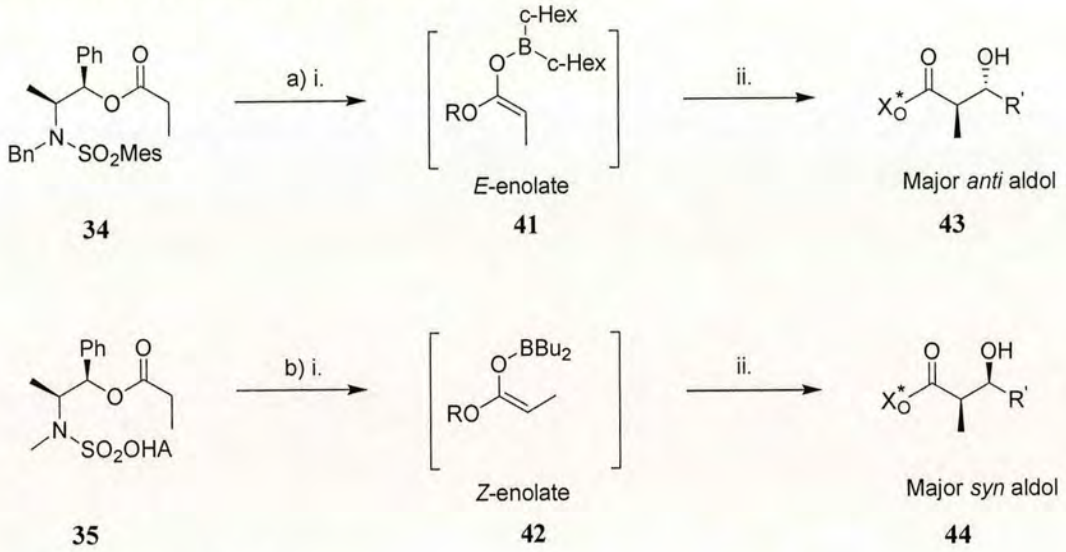
Figure 4: Optimum Masamune auxiliaries for *anti*- and *syn* aldol reactions.[32,33]

Both enantiomers of the propionate esters **34** and **35** (**figure 4**) can be prepared from commercially available (+)- or (-)-norephedrine and (+)- or (-)-ephedrine respectively in three steps: selective sulfonylation of the amino group, selective *N*-alkylation and acylation with propionyl chloride and pyridine (**scheme 11**).



Scheme 11: Synthesis of acylated Masamune chiral auxiliaries.[30-33] Reagents and conditions: a) $MesSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C to RT, 100%. b) BnBr, K_2CO_3, MeCN, reflux, 95%. c) and e) EtCOCl, pyridine, CH_2Cl_2, 0 °C to RT, 100%. d) $OHASO_2Cl$, Et_3N, CH_2Cl_2, 0 °C to RT, 95%.

Abiko[33] has shown that the aldol reaction of propionate chiral esters **34** and **35** (**figure 4**) with a wide variety of aldehydes proceeds *anti*- or *syn*-selectively by the judicious selection of the enolisation reagents. Treatment of propionate esters with dicyclohexylboron triflate and triethylamine produces *anti*-aldol products, and with dibutylboron triflate and diisopropylethylamine gives *syn*-aldol products selectively after reaction with aldehydes (**scheme 12**).



Mes = 2,4,6-trimethylphenyl.

OHA = 1,2,3,4,6,7,8,9-octahydroanthracenyl.

Scheme 12: Optimal conditions for *anti* and *syn* aldol reactions.[33] Reagents and conditions: a) i. c-Hex_2BOTf (2.0 eq.), Et_3N (2.4 eq.), CH_2Cl_2, -78 °C; ii. R'CHO (1.2 eq.), -78 °C to 0 °C. b) i. Bu_2BOTf (2.0 eq.), $^iPr_2NEt$ (2.4 eq.), CH_2Cl_2, -78 °C; ii. R'CHO (1.5 eq.), -78 °C to 0 °C.

Many natural products often contain both *anti*- and *syn*-β-hydroxy-α-methylcarbonyl units in their structural framework.

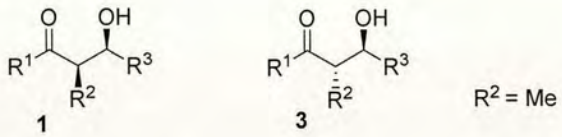
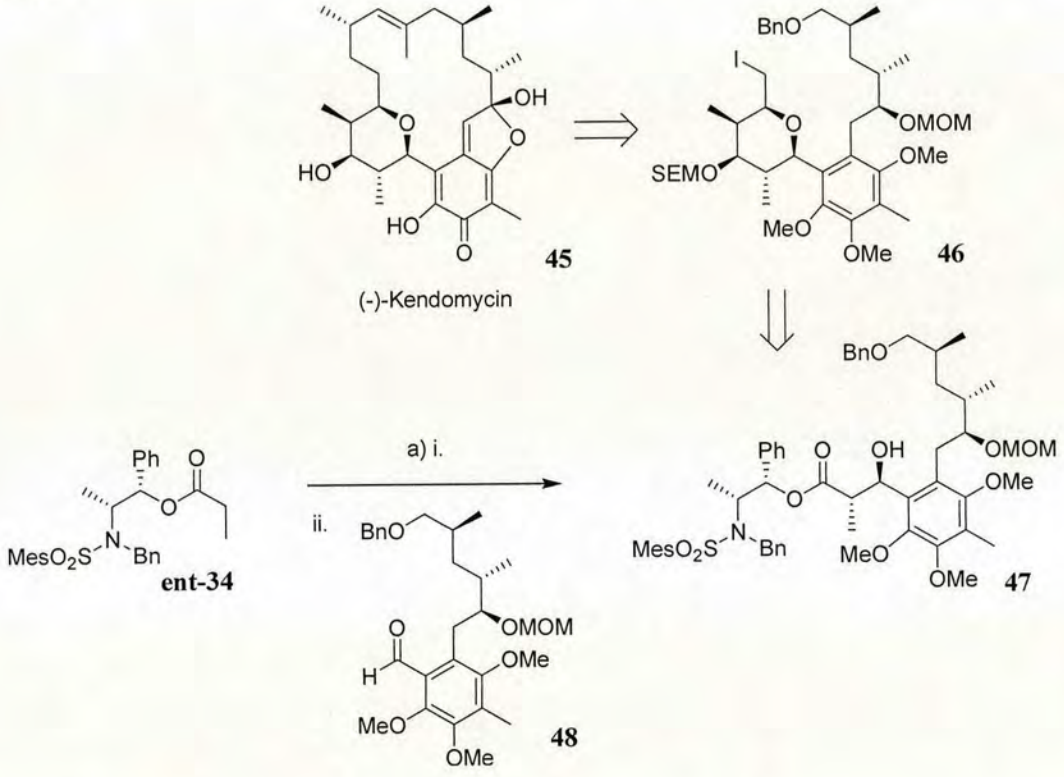


Figure 5: *Syn*- and *anti*-β-hydroxy-α-methylcarbonyl compounds.

The *anti*-selective aldol reaction using chiral propionate esters derived from norephedrine represents one of the most reliable and practical methods for the direct construction of the *anti*-β-hydroxy-α-methylcarbonyl systems,[30-34] which has challenged synthetic chemists in the aldol field for many years. Several applications to natural product synthesis have been reported in recent years.[43-50]

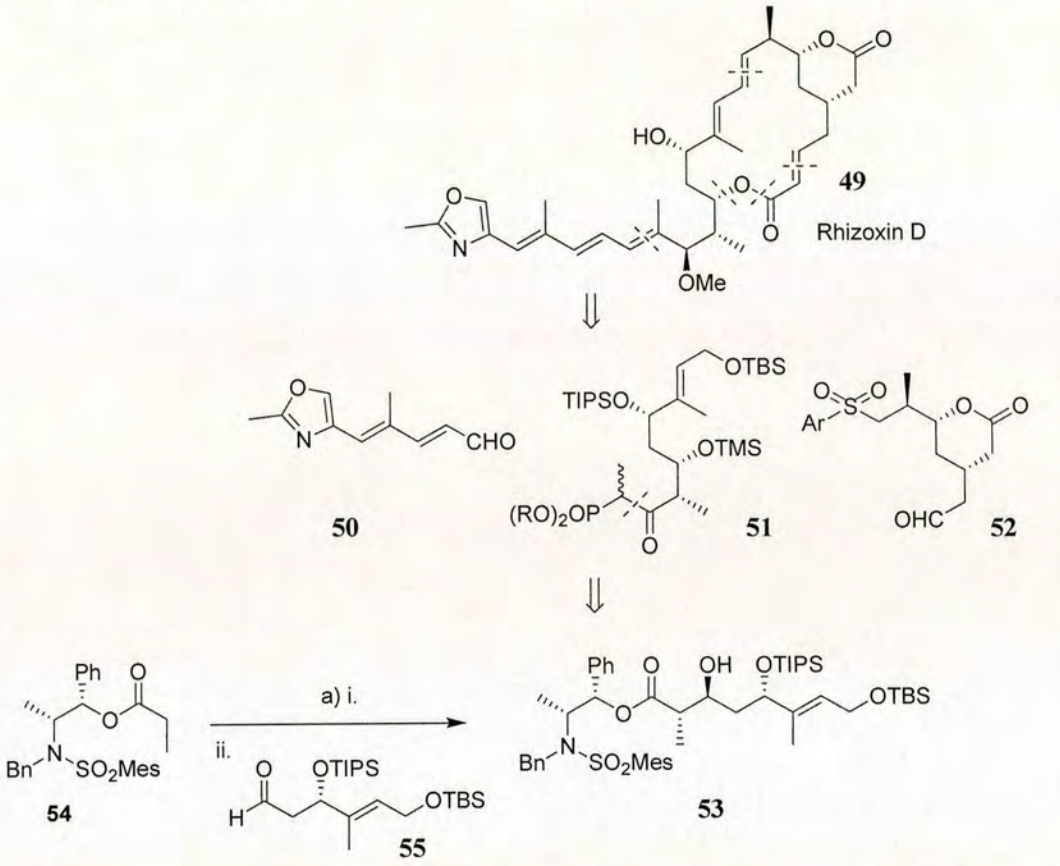
White[43] has used the Masamune chiral auxiliary to produce an *anti* aldol fragment **47** in his synthesis of a major portion of (-)-kendomycin (**scheme 13**), which has been reported to posses antibacterial and cytostatic activity.[51,52] The unique structure of (-)-kendomycin **45**, in which an ansa macrocycle incorporating a fully-substituted tetrahydropyran, bridges a quinone methide core, presents a challenging target for synthesis.[53] Towards that goal, White has established a route to synthesise a major portion **46** of (-)-kendomycin (**scheme 13**), including seven of its nine stereogenic centres.



Scheme 13: Use of the Masamune auxiliary towards the synthesis of (-)-kendomycin.[43] Reagents and conditions: a) i. c-Hex_2BOTf, Et_3N, CH_2Cl_2, -78 °C; ii. **48**, -78 °C to 0 °C (71%, ds >97:3).

In the synthesis of **46** an *anti*-selective boron-mediated aldol reaction was used. Aldehyde **48** (**scheme 13**) was too sterically hindered for reactions intended to install a precursor to the tetrahydropyran segment of **46**. These included asymmetric crotylation[54] as well as Evans' *anti*-selective aldol process.[55] Oppolzer's sultam methodology[56] was only slightly more successful, but the reaction of aldehyde **48** with the dicyclohexylborinate of propionate **ent-34** led smoothly to hydroxy ester **47** in high diastereoselectivity (>97:3).

Leahy[45] has also used the Masamune methodology in his enantioselective total synthesis of the antitumor macrolide rhizoxin D **49**. Leahy's retrosynthetic analysis (**scheme 14**) shows how the central core of rhizoxin D can be prepared via a chiral asymmetric aldol protocol.



Scheme 14: Use of the Masamune auxiliary towards the synthesis of rhizoxin D.[45] Reagents and conditions: a) i. c-Hex_2BOTf, Et_3N, CH_2Cl_2, -78 °C; ii. **55**, -78 °C to 0 °C (81%, ds >95:5).

During his work an efficient *anti*-selective aldol reaction was needed to install the natural stereochemistry. Synthesis of fragment **51** began from aldehyde **55** (**scheme 14**), which was studied extensively as the substrate for an *anti*-aldol reaction. Paterson,[57] Heathcock,[58] Duthaler[59] and Oppolzer[56] protocols failed to give the desired aldol adduct **53** in good yield and/or diastereoselectivity. In particular, it was found that loss of the primary silyl protecting group or elimination of the protected hydroxyl β to the carbonyl were recurring problems. Fortunately during the course of Leahy and co-workers studies Masamune and co-workers introduced the norephedrine-derived auxiliary methodology to give *anti* aldol products,[30-33] which worked quite well on Leahy's substrate, giving excellent diastereoselectivity (ds > 95:5) and yield (81%).

Furstner carried out the total synthesis of glucolipsin A (**figure 6**), a complex glycolipid with glucokinase-activating properties, by using auxiliary guided aldol reactions.[46]

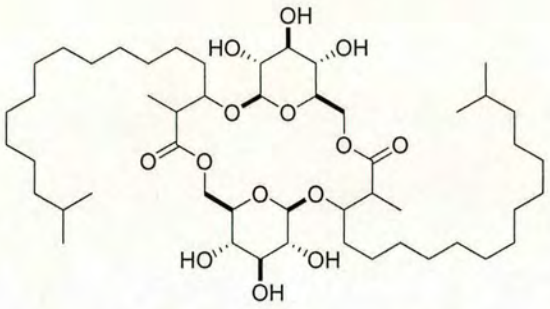
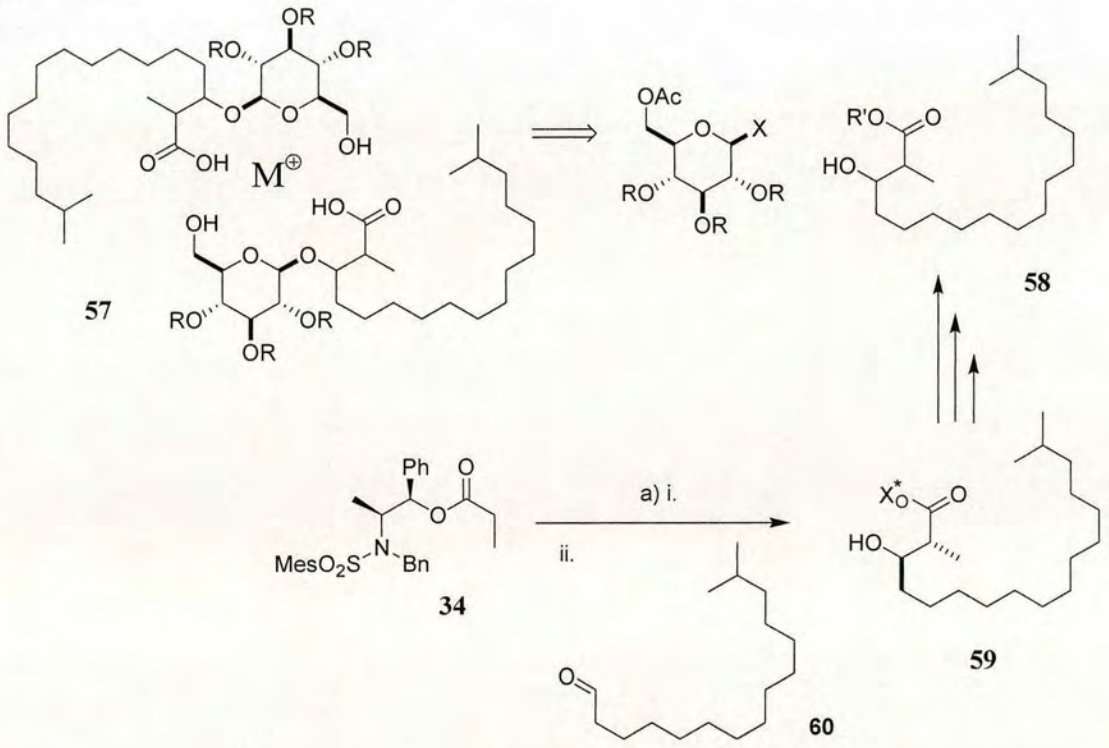


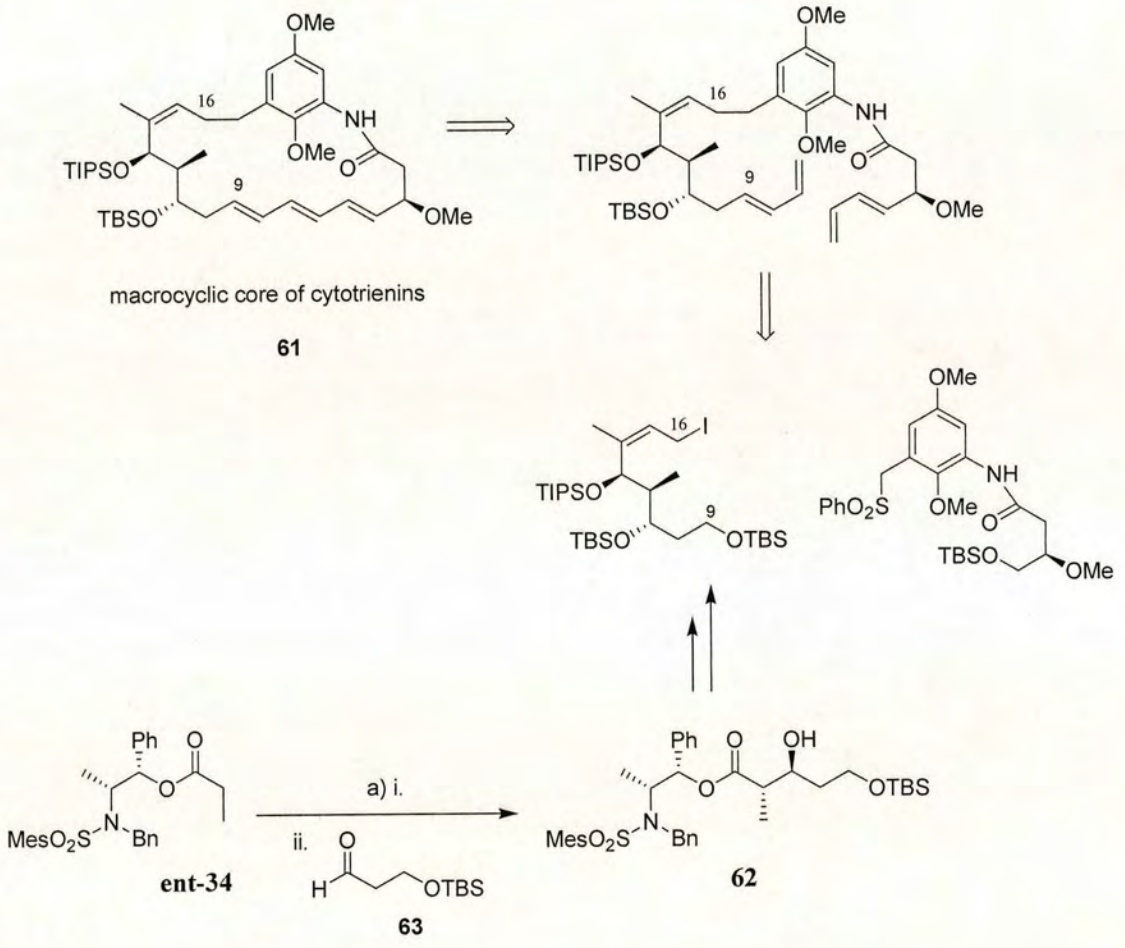
Figure 6: Glucolipsin A.

Furstner's retrosynthetic key strategy (based on the specific array of oxygen atoms in the core region of glucolipsin A) assumed the assembly of the target via a template-directed macrodilactonisation reaction of a glycosylated aldol derivative **57** preorganised around a suitable metal cation (**scheme 15**). In the preparation of building block **58**, the norephedrine-derived auxiliary was employed to give the desired *anti*-aldol derivative **59** (**scheme 15**) in good yield (71%) and excellent diastereoselectivity (ds > 99:1).



Scheme 15: Use of the Masamune auxiliary towards the synthesis of glucolipsin A.[46] Reagents and conditions: a) i. c-Hex_2BOTf, Et_3N, CH_2Cl_2, -78 °C; ii. **60**, -78 °C to 0 °C (71%, ds >99:1).

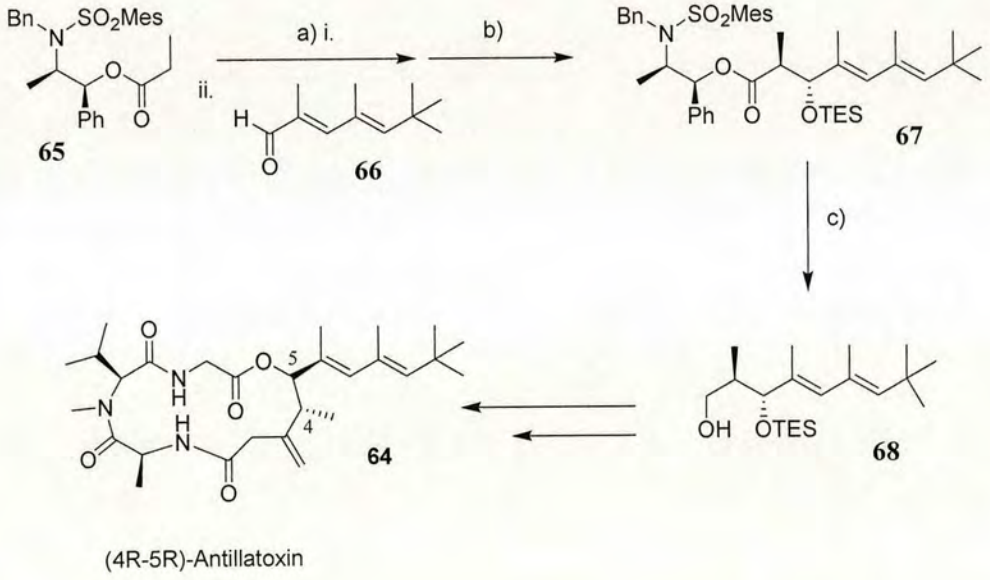
Panek[47] has reported a convergent synthesis of the highly functionalised macrocyclic core of the cytotrienins **61**, in which the synthesis of the C9-C16 fragment proceeds via an *anti*-aldol reaction. Use of the Masamune[30-34] *anti*-selective methodology leads to the formation of **62** (**scheme 16**) as a single diastereoisomer (ds > 98:2) in high yield (94%).



Scheme 16: Use of the Masamune auxiliary towards the synthesis of cytotrienins.[47] Reagents and conditions: a) i. c-Hex_2BOTf, Et_3N, CH_2Cl_2, -78 °C; ii. **63**, -78 °C to 0 °C (94%, ds >98:2).

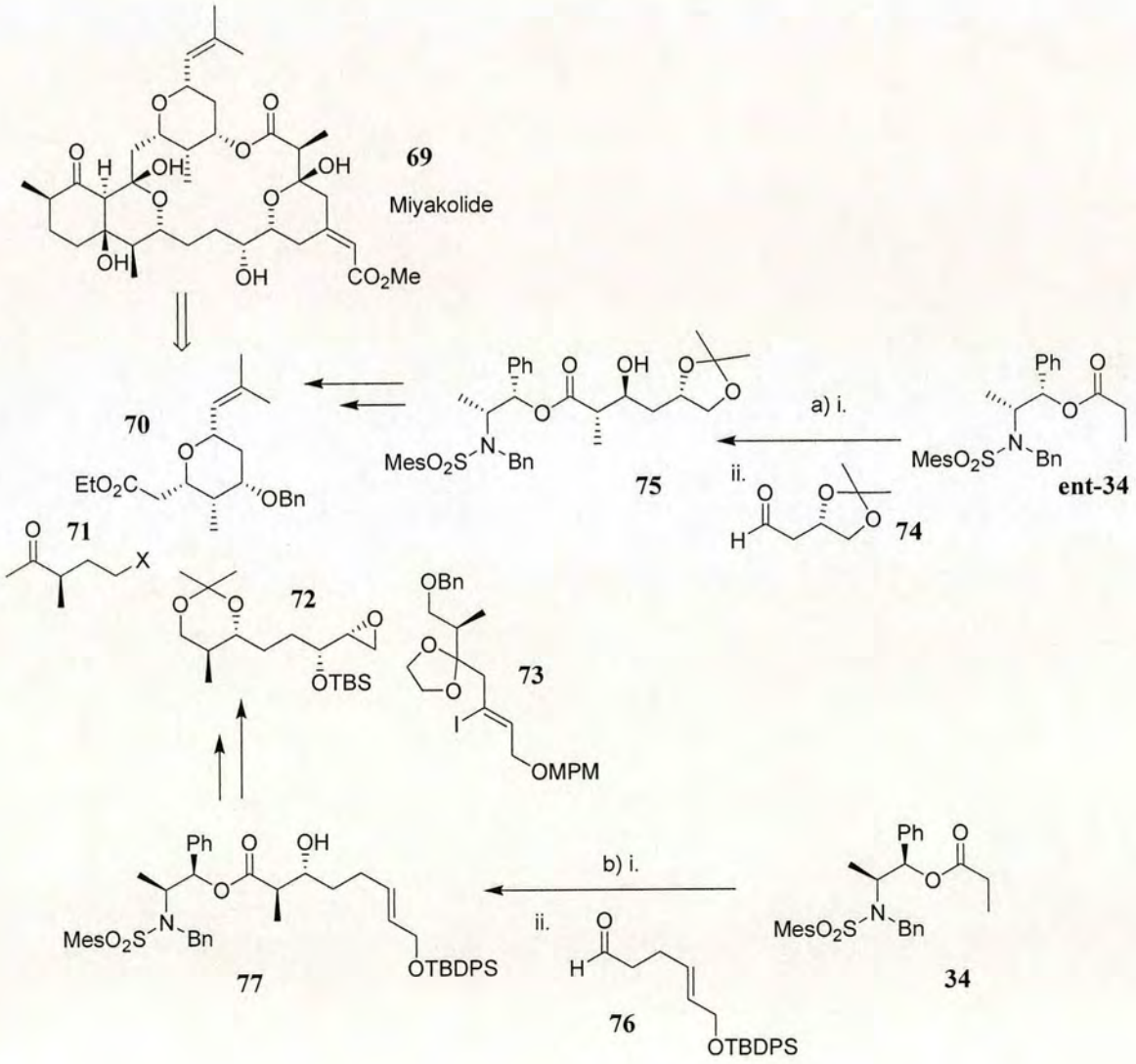
Shiori[48] and co-workers have achieved the total synthesis of the ichthyotoxic cyclic lipopeptide (4*R*,5*R*)-antillatoxin **64** (**scheme 17**) in an enantioselective convergent manner using the Abiko-Masamune[30-34] asymmetric aldol reaction.

For the construction of the *anti*-C4, C5 configuration, the *anti*-selective boron-mediated asymmetric aldol reaction developed by Abiko and Masamune was used (**scheme 17**). Aldehyde **66** was added to the *E*-enolate solution, which was generated from the propionate ester of norephedrine derivative **65** using dicyclohexylboron triflate and triethylamine. Subsequently, protection of the secondary alcohol gave the *anti*-aldol adduct **67**, which was converted into the corresponding alcohol **68** using a DIBAL reduction.



Scheme 17: Use of the Masamune auxiliary for the synthesis of (4*R*-5*R*)-antillatoxin.[48] Reagents and conditions: a) i. c-Hex_2BOTf, Et_3N, CH_2Cl_2, -78 °C; ii. **66**, -78 °C to 0 °C b) TESOTf, 2,6-lutidine, $CHCl_3$ (90%, 2 steps). c) DIBAL, CH_2Cl_2, 100%.

Masamune[49] has also used his own *anti*-selective aldol methodology in the synthesis of two key fragments **70** and **72** of miyakolide **69** (**scheme 18**) via asymmetric aldol reactions. The synthesis of fragment **70** starts from the chiral aldehyde **74** (**scheme 18**) which reacts with the propionate chiral ester **ent-34** derived from (1*S*,2*R*)-norephedrine to give the aldol adduct **75** in high yield (90%) and good diastereoselectivity (>94:6). Construction of fragment **72** involves another *anti*-selective aldol reaction; aldehyde **76** was treated with the chiral ester **34** derived from (1*R*,2*S*)-norephedrine to give the aldol product **77** in 85% yield with good selectivity (>94:6).

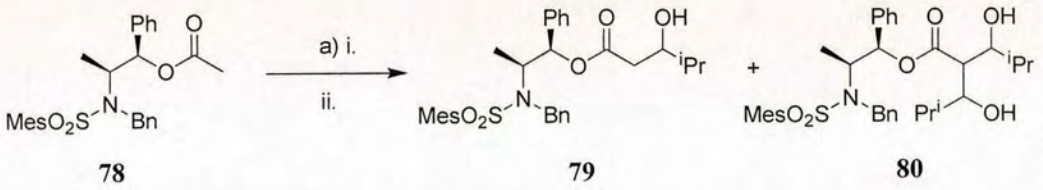


Scheme 18: Use of the Masamune auxiliary towards the synthesis of miyakolide.[49] Reagents and conditions: a) i. c-Hex_2BOTf, Et_3N, CH_2Cl_2, -78 °C; ii. **74**, -78 °C to 0 °C (90%, ds >94:6). b) i. c-Hex_2BOTf, Et_3N, CH_2Cl_2, -78 °C; ii. **76**, -78 °C to 0 °C (85%, ds >94:6).

All these examples show how the Masamune auxiliary can be effectively used in the construction of a variety of substrates, to obtain *anti*-aldol adducts with a wide range of aldehydes: from aromatic (*e.g.* **scheme 13**), to vinyl (*e.g.* **scheme** 17) or alkyl (*e.g.* **scheme 15**), achieving high yields and diastereoselectivities.

1.2.2 Acetate Aldol Reactions

An extension of the Masamune methodology includes an acetate aldol reaction utilising chiral ester **78**. Treatment of **78** under the known conditions necessary to obtain mono-aldol propionate derivatives in high yield (**scheme 12**), provides bis-aldol products **80** via a double aldol reaction, along with the expected mono-aldol product **79**.[60-62]



Scheme 19: Double aldol reaction. Reagents and conditions: a) i. c-Hex_2BOTf (2.5 eq.), Et_3N (3.0 eq.), CH_2Cl_2, -78 °C; ii. ^iPrCHO (3.0 eq.), -78 °C to 0 °C.

Efforts to optimise the conditions for almost exclusive formation of bis-aldol products (**scheme 19**), led to the formation of **80** in over 95% yield with a diastereoisomer ratio of **80a : 80b : 80c** = 90 : 8 : 2 (**figure 7**). The fourth possible isomer was not detected.

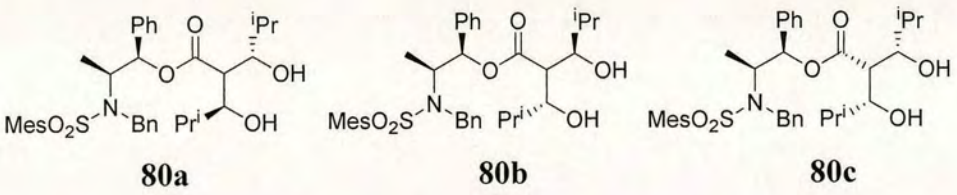
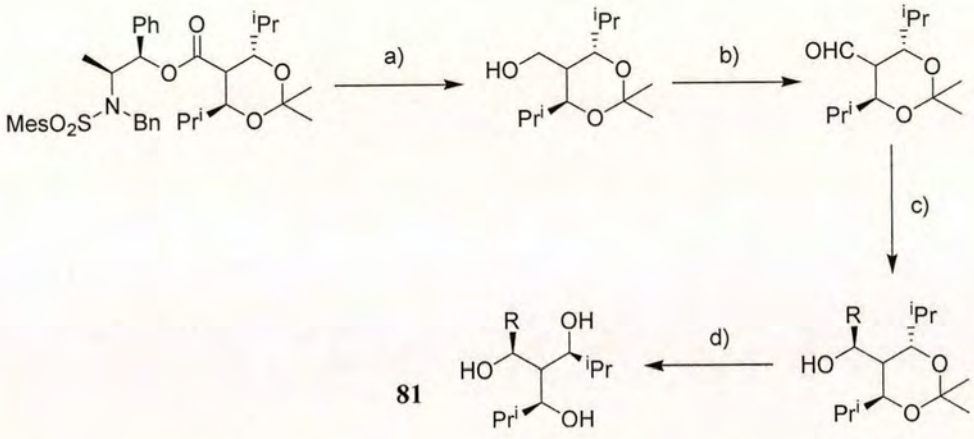


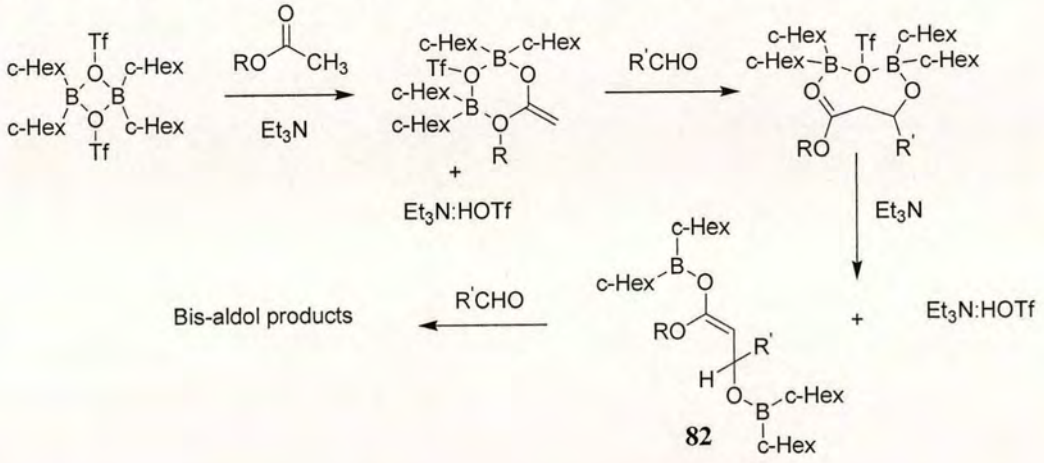
Figure 7: Bis-aldol stereoisomers.

These bis-aldol products serve as the starting material for the synthesis of chiral triols **81** of C_3 symmetry (**scheme 20**). Compounds of C_3 symmetry have attracted much attention as valuable ligands for asymmetric catalysts.[63,64]



Scheme 20: Bis-aldol products as starting material for chiral triols of C_3 symmetry. Reagents and conditions: a) $LiAlH_4$, THF (99%). b) PDC, CH_2Cl_2 (95%). c) RMgX, THF (65%, 97:3). d) TFA, MeOH, (96%).

While double aldol reactions proceed with acetate esters, this double reaction does not occur with other carbonyl compounds such as methyl ketones, acetate thiolesters and propionate esters. There is the possibility that two kinds of boron species are involved in the boron-mediated aldol reaction.[60-62] The first boron species exists with ketones and thiolesters and leads to the single aldol reaction, since boron can only chelate with the carbonyl group to form a 1:1 complex. The second boron species exists with acetate esters, in which coordination to the extra oxygen atom forms a 2:1 complex **82** (**scheme 21**), which leads to the double aldol reaction. The failure of the double aldol reaction for propionate esters can probably be attributed to steric reasons.[34]



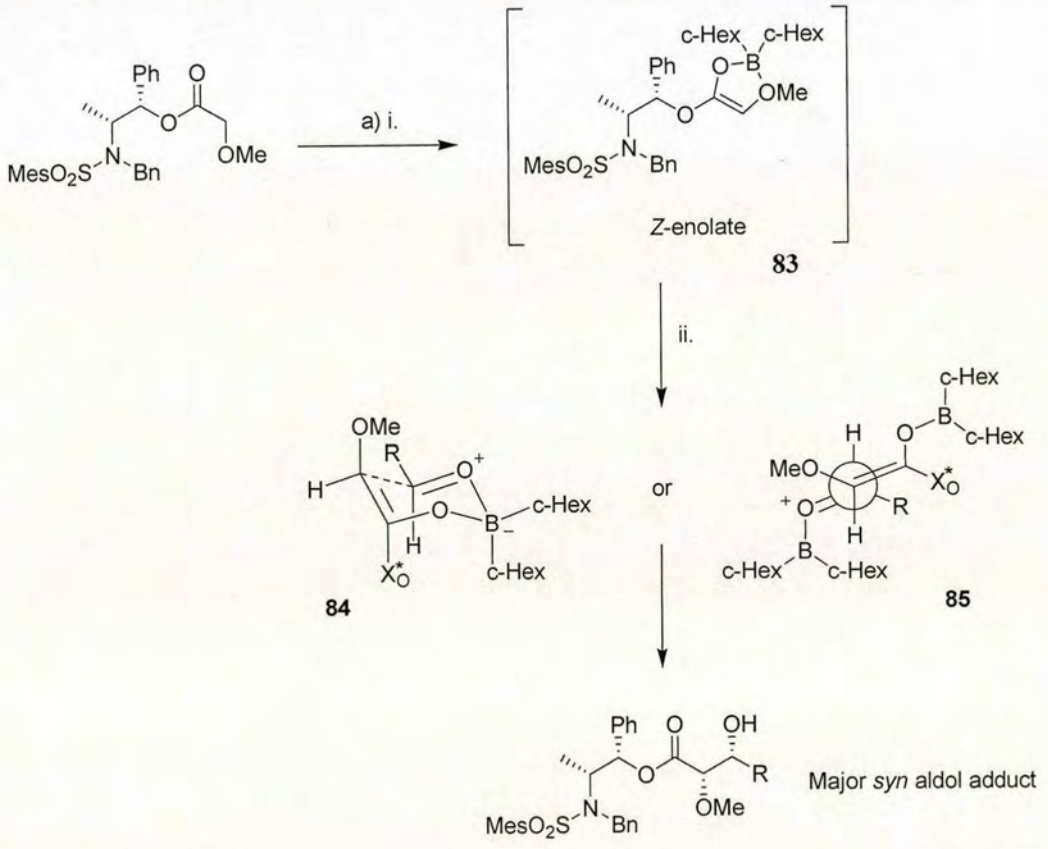
Scheme 21: Possible pathway in the formation of bis-aldol products.[60]

1.2.3 Glycolate Aldol Reactions

Aldol reactions have been extensively used in synthesis to produce differently protected 1,2-diol products. Various approaches have been undertaken, in most cases involving *syn* outcomes using a boron enolate of Evans' oxazolidin-2-one glycolate.[26-29]

There are also examples in the literature of highly selective *syn* glycolate aldol reactions with boron enolates of Masamune norephedrine esters.[65-67] In contrast to the propionate series (**scheme 12**), in this case the optimal conditions to produce the *syn* product were dicyclohexylboron triflate and triethylamine (**scheme 22**).

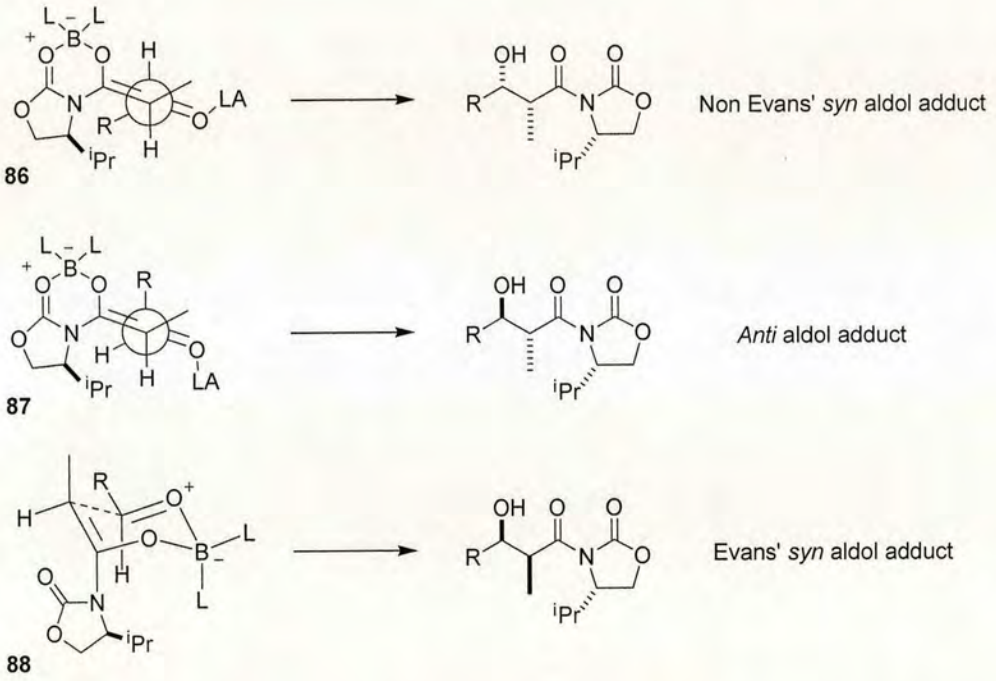
The glycolate *syn* aldol pathway begins with *Z*-enolate formation. The boron can chelate with two oxygen atoms forming a five-membered ring coordinated enolate **83**, overcoming any steric effects imposed by the ligands on boron. After addition of aldehyde two options for product formation can be considered,[65] the reaction could proceed via a closed transition state **84** or an open arrangement **85** (**scheme 22**).



Scheme 22: Glycolate *syn* aldol pathway.[65] Reagents and conditions: a) i. c-Hex$_2$BOTf (3.0 eq.), Et_3N (2.5 eq.), CH_2Cl_2, -78 °C; ii. RCHO (1.2 eq.), -78 °C to 0 °C.

Heathcock[68-70] has reported that Evans' oxazolidinones can lead to the formation of *anti*-aldol adducts when an excess of triflate is present. Under these conditions the reaction occurs through an open transition state in which the triflate, acting as a Lewis acid, forms an activated complex with the aldehyde (**scheme 23**).

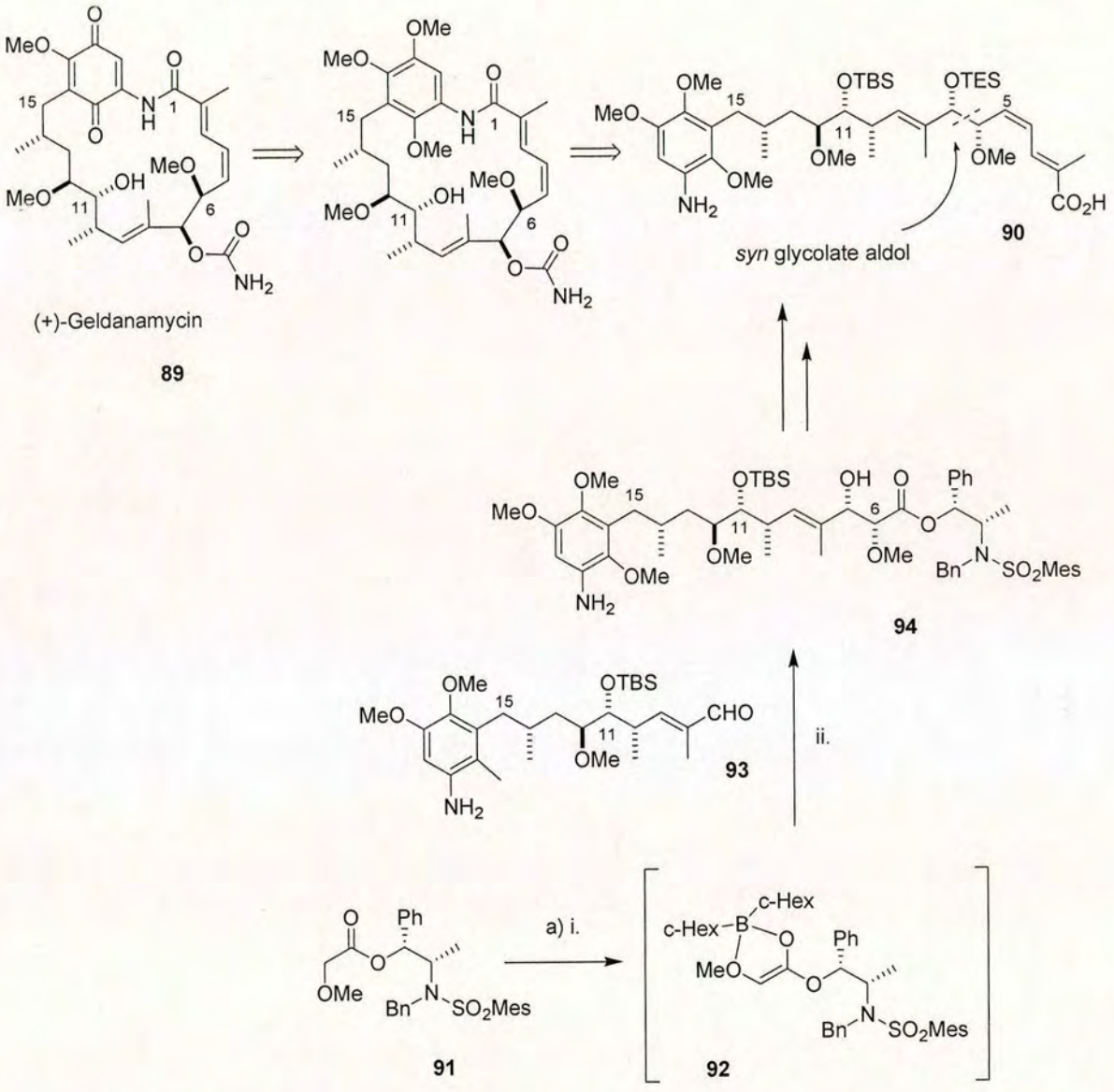
Two possible open arrangements can be formed. Complex **86** is preferred with small Lewis acids (*e.g.* $SnCl_4$, $TiCl_4$) because it minimizes gauche interactions about the forming bond. In contrast, large Lewis acids (*e.g.* Et_2AlCl, Bu_2BOTf, c-Hex_2BOTf) favour complex **87** due to the methyl-Lewis acid interaction in **86**. In the absence of an excess of the triflate, the reaction takes place via a Zimmerman-Traxler transition state **88**, to afford the Evans *syn* aldol adduct as the major product (**scheme 23**).



Scheme 23: Open and close transition states with Evans' oxazolidinones.[68,69]

Under all conditions investigated with the glycolate-Masamune substrate, including various quantities of different boron compounds and bases,[65] only *syn* products were obtained. Thus, the reaction proceeds through a close transition state, as partitioning to other diastereoisomers would be seen, if open arrangements with excess boron triflate Lewis acid activation were operative.

Andrus[65-67] and co-workers have applied their own methodology for the construction of *syn*-glycolate aldol units in the total synthesis of (+)-geldanamycin **89** (**scheme 24**),[66,67] an antitumor Hsp90 inhibitor that shows broad activity with the NCI 60 cell-line panel (13 nM).[71,72]



Scheme 24: *Syn* glycolate aldol reaction using Masamune-based methodology.[66,67] Reagents and conditions: a) i. c-Hex$_2$BOTf, Et$_3$N, CH$_2$Cl$_2$, -78 °C; ii. **93**, -78 °C to 0 °C (90%, ds> 20:1).

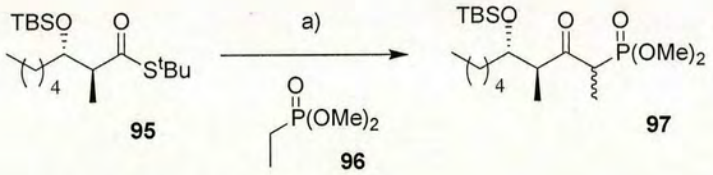
Synthesis of fragment **90** involved a *syn*-selective glycolate aldol reaction. The boron enolate **92** of the norephedrine-based glycolate **91** reacted with aldehyde **93** to generate **94** in greater than 20:1 diastereoselectivity and 90% isolated yield (**scheme 24**). In contrast, asymmetric aldol reaction using the well-known methylglycolate oxazolidinone boron enolate[29] gave a much reduced 2:1 mixture of diastereomeric *syn* aldol products.

1.3 AN ALTERNATIVE STRATEGY: A NEW SULFUR MASAMUNE DERIVATIVE

For an auxiliary-based strategy to be truly useful, the auxiliary must be removable under a range of conditions. Although this has been demonstrated to a certain extent for the Evans' oxazolidinone and the Abiko-Masamune auxiliary, there are still some nucleophilic displacement reactions which, though highly desirable synthetically, are unachievable or very low yielding with either of these auxiliaries, due to competitive retro-aldol or elimination reactions.

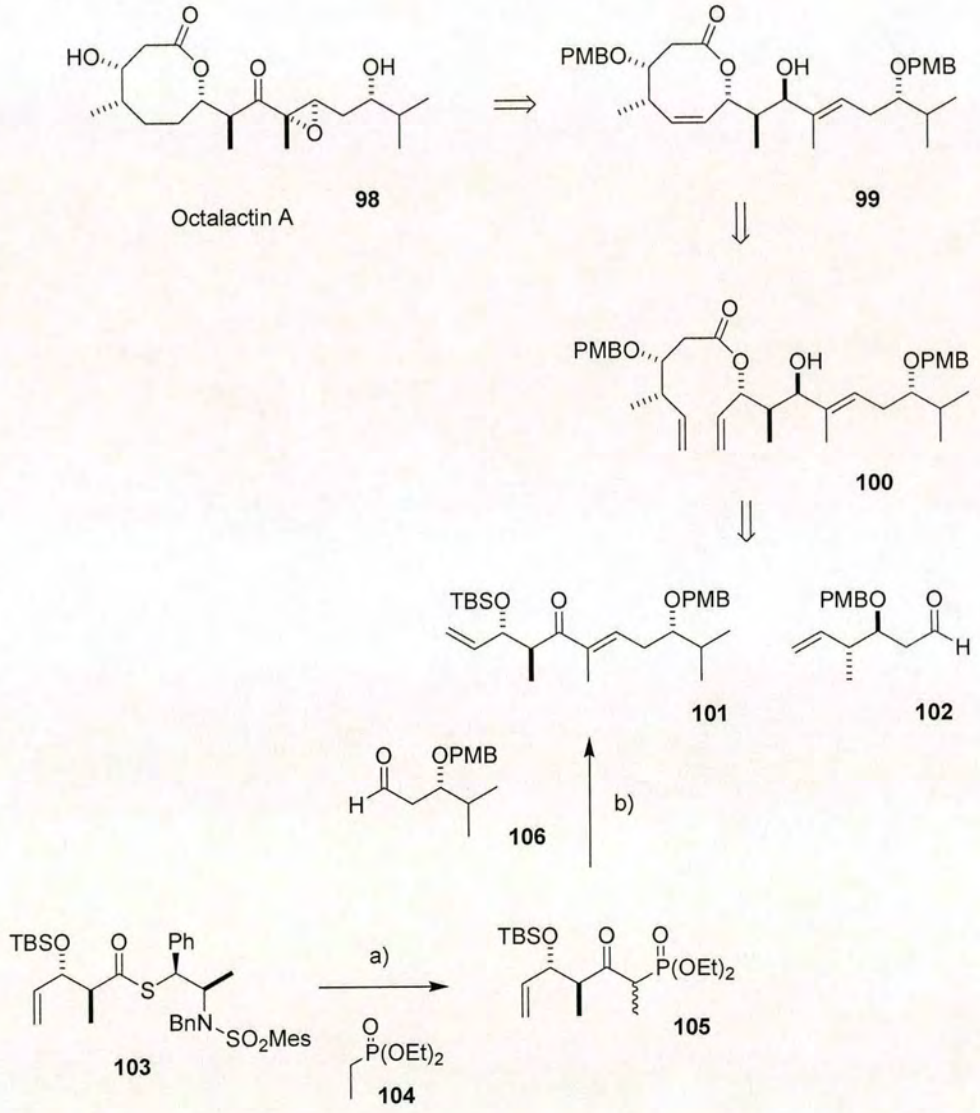
Previous studies within the Hulme group[73,74] and several examples in the literature[75-80] have shown that thiolesters can be easily displaced using mild conditions.

An efficient synthesis of *β*-ketophosphonates **97** from *tert*-butyl thiolesters **95** using the lithium anion of either methane- or ethane-phosphonate has been described previously within the Hulme group (**scheme 25**).[73]



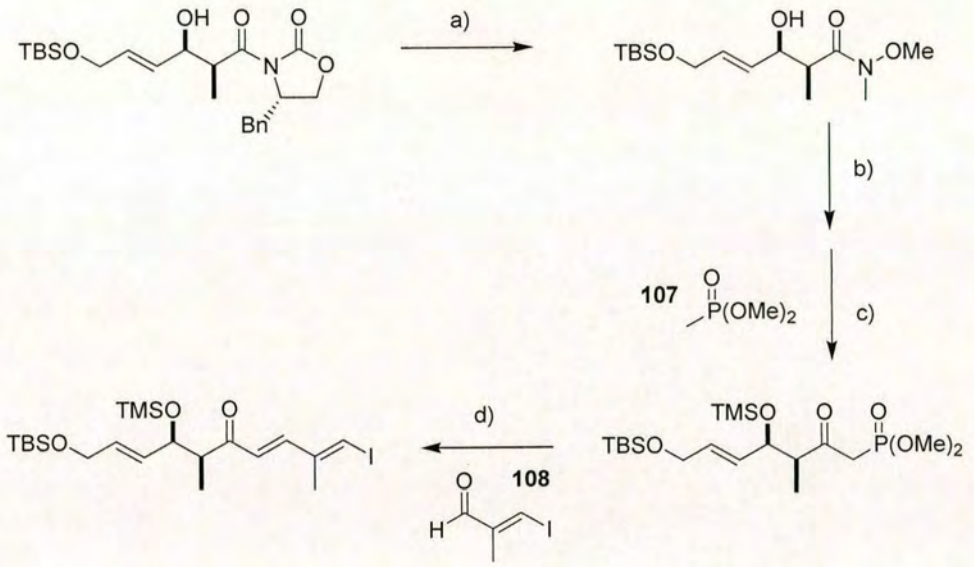
Scheme 25: Synthesis of *β*-ketophosphonates from thiolesters.[73] Reagents and conditions: a) **96**, BuLi, THF, -78 °C (73%).

This mild phosphonate displacement approach has been used in the studies towards the synthesis of marine metabolite octalactin A (**scheme 26**).[74] In the synthesis of key target **101** a phosphonate displacement on aldol adduct **103** was carried out to give **105** in good yield. This could be converted via the HWE reaction to enone **101** (**scheme 26**).



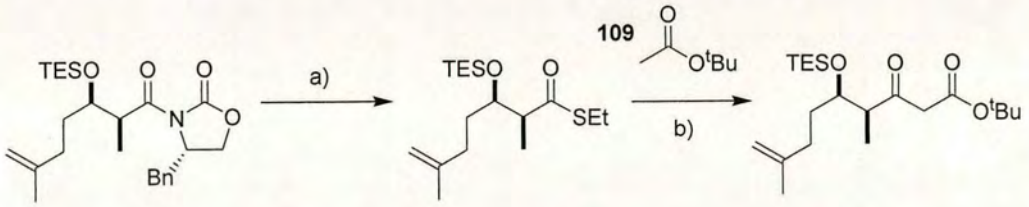
Scheme 26: Phosphonate displacement of a thiolester in the synthesis of octalactin A.[74] Reagents and conditions: a) **104**, BuLi, THF, -78 °C, (81%). b) **106**, $Ba(OH)_2$, THF (aq.) (81%).

As described above the displacement was readily undertaken onto the thiolester aldol adduct. In contrast, Evans' oxazolidinone aldol substrates are usually converted to the corresponding Weinreb amides, in order to achieve the desired phosphonate displacement prior to a HWE reaction (as shown in **scheme 27**).[76]



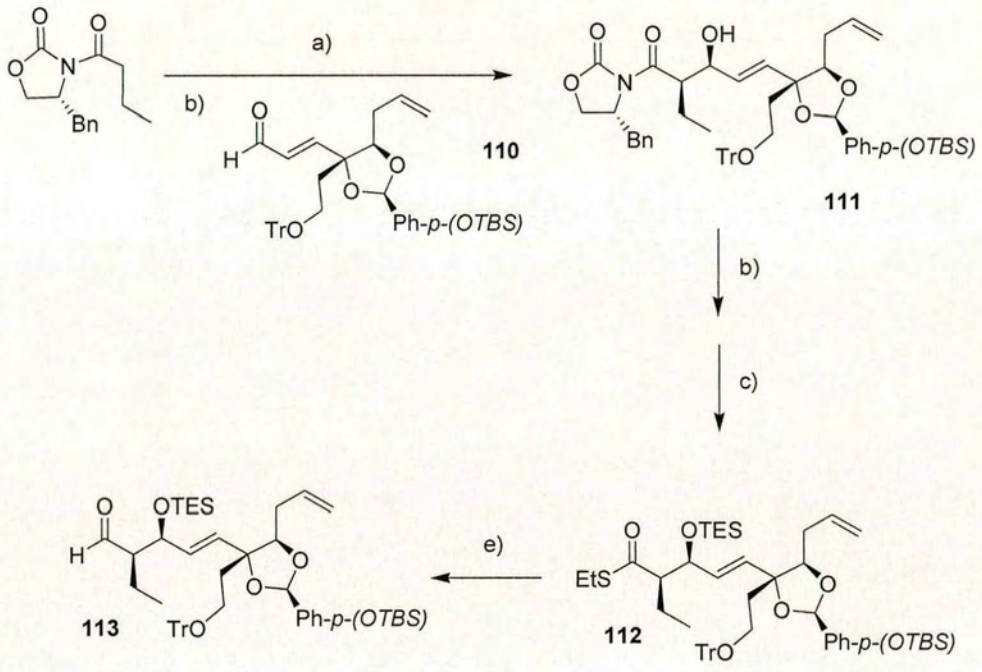
Scheme 27: Phosphonate displacement of Evans' oxazolidinones.[76] Reagents and conditions: a) Me_3Al, MeONHMe•HCl, THF, 0 °C (75%). b) TMSCl, Imidazole, DMAP, CH_2Cl_2. c) **107**, BuLi, THF, -78 °C. d) **108**, $Ba(OH)_2$, THF (aq.), 0 °C (79% over three steps).

There are many other examples in the literature where oxazolidinone aldol substrates are converted into thiolesters to carry out transformations not allowed directly on the aldol adduct. In the enantioselective synthesis of FR182877 by Sorensen,[76] a Claisen condensation type displacement was attained under very mild conditions using a thiolester (**scheme 28**).



Scheme 28: Mild displacement by Claisen condensation.[76] Reagents and conditions: a) LiSEt, THF, -78 °C. b) **109**, LDA, THF, -78 °C to 0 °C (71% over two steps).

In the total synthesis of Leustroducsin B by Fukuyama,[75] mild reduction conditions were used to reduce thiolester **112** to aldehyde **113**.



Scheme 29: Mild reduction to aldehyde **113**.[75] Reagents and conditions: a) Bu_2BOTf, $^iPr_2EtN$, CH_2Cl_2, -78 °C. b) **110**, -78 °C to 0 °C. c) TESCl, Imidazole, DMF. d) LiSEt, THF, 0 °C (72% over three steps). e) DIBAL, toluene, -78 °C.

It is also known that using sulfur derivatives of Evans' oxazolidinones the removal of the auxiliary proceeds under milder conditions.[82-90]

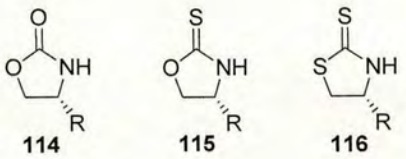
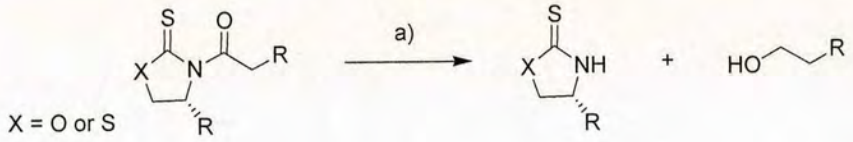


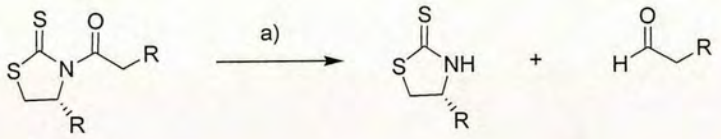
Figure 8: Evans' oxazolidinone and its sulfur counterparts.

Both *N*-acyl oxazolidinethiones **115** and thiazolidinethiones **116** can be reductively removed with either lithium or sodium borohydride in good yields, to produce primary alcohols and release the oxazolidinethione and thiazolidinethione auxiliaries (**scheme 30**).[82-89]



Scheme 30: Easy reductive cleavage of oxa- and thiazolidinethiones. Reagents and conditions: a) $NaBH_4$ or $LiBH_4$, THF/EtOH, 0 °C.

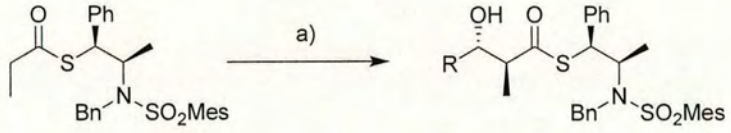
Most importantly, thiazolidinethiones **116** can be directly converted to the corresponding aldehydes, and release the chiral auxiliary, by reductive cleavage with diisobutylaluminum hydride (**scheme 31**).[82-88]



Scheme 31: Direct conversion to aldehydes. Reagents and conditions: a) DIBAL, CH_2Cl_2, -78 °C.

Many other transformations, such as: ester formation,[85-90] hydrolysis[84-87] or aminolysis,[85-88] occur under milder conditions than those needed with oxazolidinones. Transamination to the Weinreb's amide can be achieved without using trimethylaluminium.[85-87]

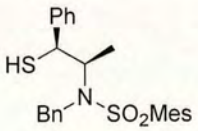
Studies carried out within the Hulme group have shown that using a thiol derivative of the Abiko-Masamune chiral auxiliary under the conditions for the *anti*-selective propionate aldol reactions (**scheme 32**), good yields and diastereoselectivities can be achieved.[91,92]



Scheme 32: Results for the *anti*-aldols using a sulfur derivative of the Masamune's auxiliary.[91,92] Reagents and conditions: a) c-Hex_2BOTf, Et_3N, CH_2Cl_2, -78 °C; then RCHO, -78 °C to 0 °C (> 81%, ds> 91:9).

Encouraged by these results we decided to investigate the use of the thiolester chiral auxiliary for *syn*-selective propionate aldol reactions and *syn*- and *anti*-selective glycolate aldol reactions.

We have also optimised the route towards the synthesis of the new thiol chiral auxiliary **117** and studied its easy removal under a range of very mild conditions.[92]



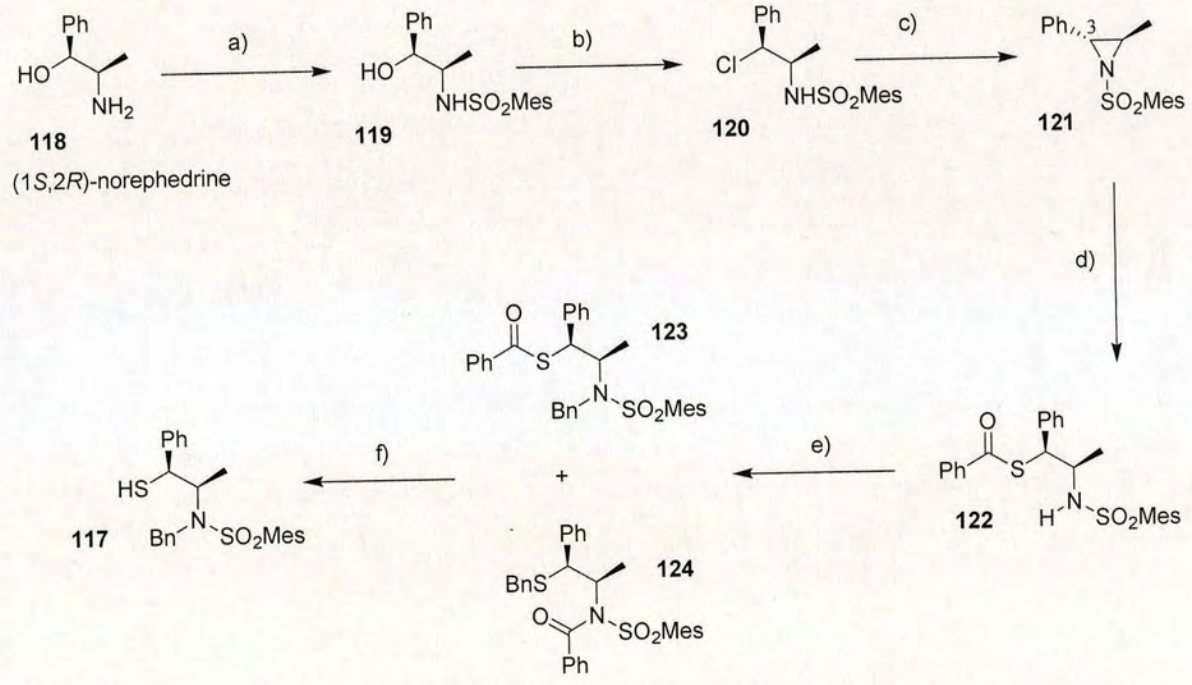
117

Figure 9: New thiol chiral auxiliary.

CHAPTER 2: RESULTS AND DISCUSSION 1

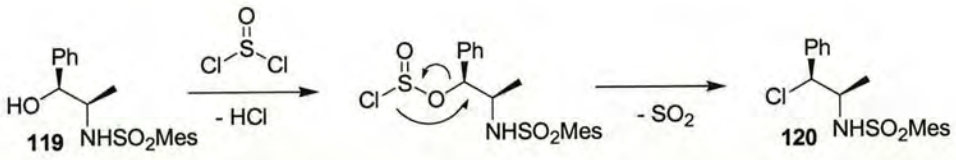
2.1 SYNTHESIS OF A SULFUR DERIVATIVE OF MASAMUNE'S AUXILIARY

The initial synthetic strategy developed by John White within the Hulme group to synthesise a sulfur derivative of the Masamune auxiliary involved a six-step high-yielding route (**scheme 33**), in which a double inversion was performed to achieve the desired stereochemistry (> 44% over 6 steps).[91]



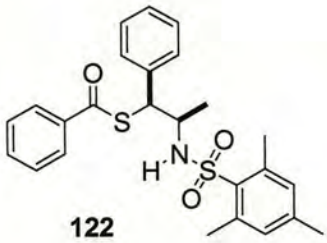
Scheme 33: Initial synthetic strategy to thiol auxiliary **117**.[91] Reagents and conditions: a) $MesSO_2Cl$, Et_3N, CH_2Cl_2, 2 h, 0 °C (95%). b) $SOCl_2$, 12 h, RT (97%). c) ^tBuOK, DMF, 12 h, RT (91%). d) PhCOSH, PBu_3 (10 mol%), $MeCN/H_2O$, 12 h, RT (93%). e) ^tBuOK, BnBr, DMF, 18 h, RT (60% of **123**, 30% of **124**). f) $LiAlH_4$, THF, 2 h, RT (95%).

Starting from the commercially available (+)-(1*S*,2*R*)-norephedrine, selective sulfonylation of the amino group using mesitylenesulfonyl chloride and triethylamine in dichloromethane for 2 h at 0 °C, gave sulfonamide **119**.[30] Chloride product **120** was obtained by treating the norephedrine sulfonamide with thionyl chloride at room temperature overnight. The reaction proceeds via an internal nucleophilic substitution (S_Ni), with retention of stereochemistry (**scheme 34**).



Scheme 34: Retention of stereochemistry via an S_Ni mechanism.

The chloride product **120** was then treated with potassium *tert*-butoxide in dimethylformamide at room temperature for 12 h to generate the aziridine **121** via an S_N2 type mechanism, with inversion of the stereochemistry at C3. The aziridine **121** was then opened[93-95] using thiolbenzoic acid as the nucleophile and a catalytic amount of PBu_3 in acetonitrile-water at room temperature, to give the thiolester **122**. The stereochemistry of **122** was confirmed by crystallographic analysis[91] (**figure 10**).



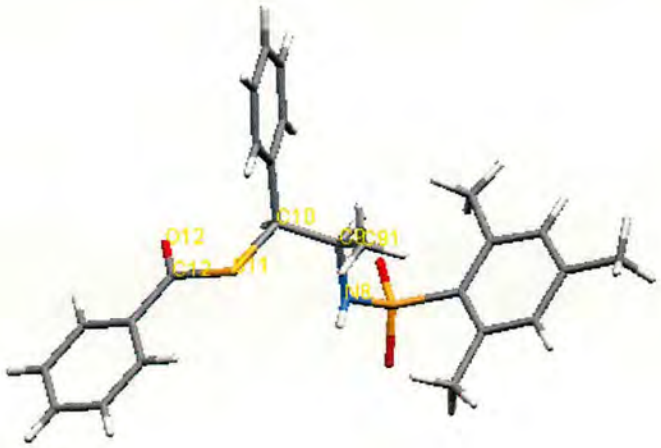
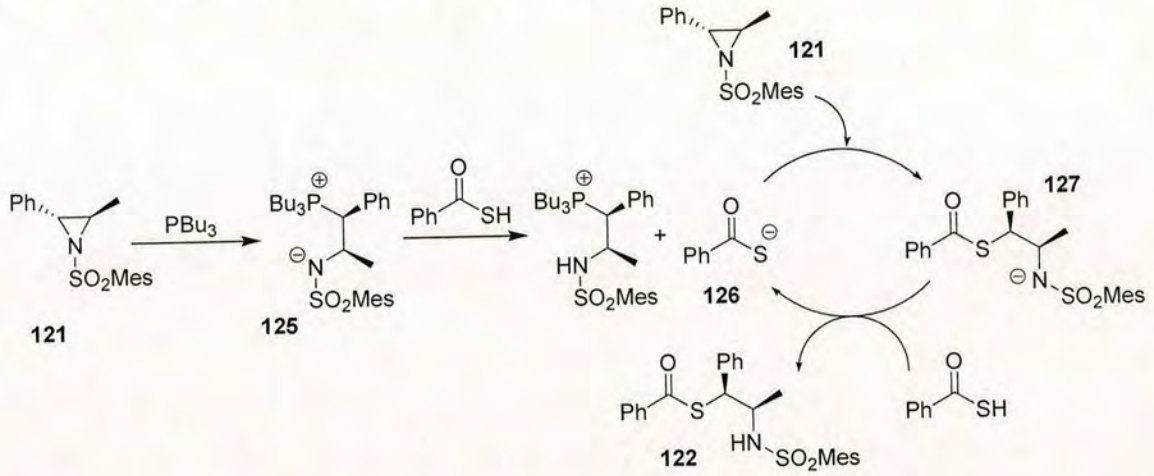


Figure 10: Crystal structure of thiolester **122**.[91]

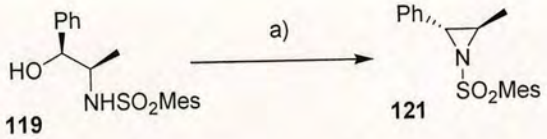
In the proposed mechanism[93-95] (**scheme 35**) the phosphine attacks the ring of the aziridine to form the salt **125**, which acts as a base to generate the anion of the nucleophile. Then the nucleophile reacts with aziridine to give the ring-opened intermediate **127**, which reacts with another nucleophile to provide the product **122** and regenerate the nucleophile **126** to complete the catalytic cycle.



Scheme 35: Proposed mechanism for the aziridine-opening reaction.[93-95]

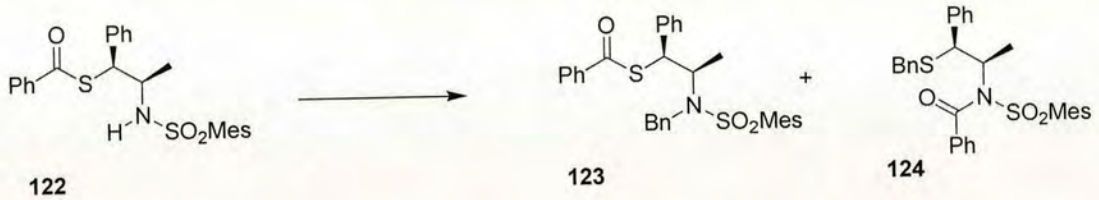
Benzylation of thiolester **122** was carried out using potassium *tert*-butoxide and benzyl bromide in dimethylformamide at room temperature. However, the desired benzylated thiolester **123** was not the only isolated product, since amide **124** generated as a result of benzyl group migration, was also detected (**scheme 33**). Finally, reduction of thiolester **123** using lithium aluminum hydride in tetrahydrofuran at room temperature generated the thiol **117** in good yield.

These preliminary studies by John White highlighted the need to optimise several steps in this initial synthetic strategy; to this end aziridine **121** was generated directly from sulfonamide **119** via formation of a mesylate intermediate. Treatment of **119** with methanesulfonylchloride in triethylamine at room temperature overnight gave the desired aziridine **121** in good yield (**scheme 36**). In this manner the use of toxic thionyl chloride was avoided and the route towards thiol **117** decreased in length by one step.



Scheme 36: Direct synthesis of aziridine **121** from sulfonamide **119**. Reagents and conditions: a) MsCl, Et_3N, 0 °C for 10 min then RT for 14 h (85%).

Efforts to optimise the benzylation step were also carried out. Treatment of thiolester **122** with potassium carbonate and benzyl bromide in acetonitrile at room temperature was unsuccessful and only starting material was recovered. However, treatment of **122** with sodium hydride and benzyl bromide in dimethylformamide at room temperature gave the desired benzylated thiolester **123** as the sole product (**table 1**).



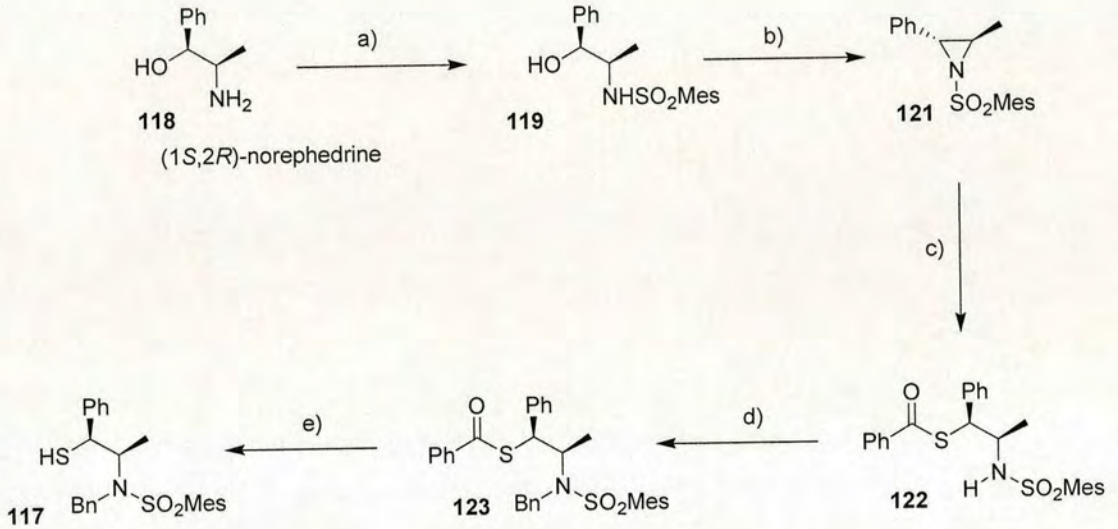
REAGENTS AND CONDITIONS	**123**	**124**
^{t}BuOK, BnBr, DMF, 18 h, RT.	60%	30%
K_2CO_3, BnBr, MeCN, 18 h, RT.	---	---
NaH, BnBr, DMF, 18 h, RT.	99%	---

Table 1: Reagents and conditions to optimise the benzylation.

While the use of potassium *tert*-butoxide gave a 30% of product **124**, migration of the benzyl group was avoided by using sodium hydride as the base. The selectivity of the reaction was controlled due to the influence of the counter ion on the nucleophilicity of the anion. While potassium generates a more ionic/nucleophilic bond with the nitrogen allowing the migration to take place, sodium gives a more covalent/less nucleophilic type of bond making selective benzylation possible. Potassium carbonate failed to give the benzylated product; because of its weaker basicity compared to potassium *tert*-butoxide, it was not able to effect the deprotonation of the sulfonamide.

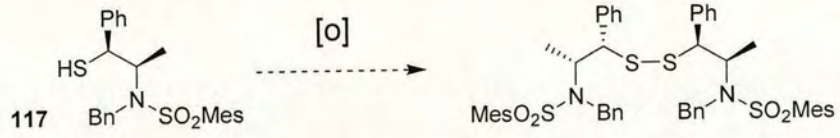
Alternative conditions to generate the thiol auxiliary **117** from benzylated thiolester **123** were also investigated. Saponification of **123** with sodium methoxide in methanol at room temperature gave thiol **117** in excellent yield, avoiding the need for tedious purification from aluminium salts when using $LiAlH_4$ (**scheme 37**).

After these results a new improved route to a thiol alternative of the Abiko-Masamune auxiliary was achieved in five steps (> 70% overall yield) from norephedrine (**scheme 37**).[92]



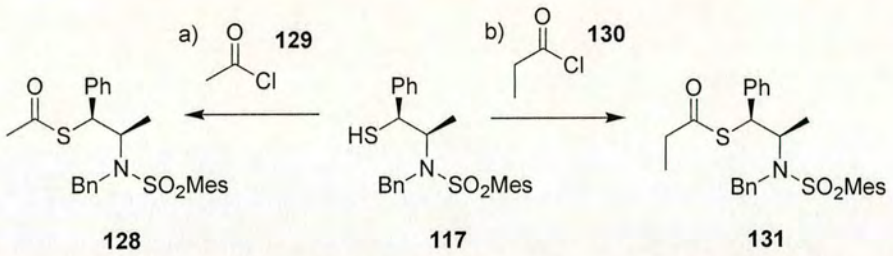
Scheme 37: Improved route towards the synthesis of the chiral auxiliary **117**.[92] Reagents and conditions: a) $MesSO_2Cl$, Et_3N, CH_2Cl_2, 2.5 h, 0 °C (95%). b) MsCl, Et_3N, 0 °C 10 min then RT for 14 h (85%). c) PhCOSH, PBu_3 (10 mol%), $MeCN/H_2O$, 18 h, RT (91%). d) NaH, BnBr, DMF, 18 h, RT (99%). e) NaOMe, MeOH, 1.5 h, RT (96%).

No aerial oxidation of the new thiol auxiliary **117** was observed when left opened to air for months in the lab, which demonstrates its high stability and therefore its ready use in synthesis (**scheme 38**).



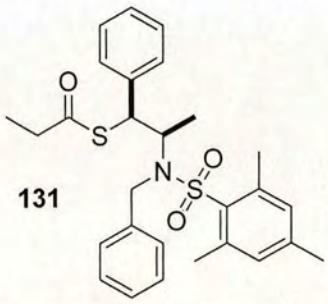
Scheme 38: No observed oxidation of thiol auxiliary **117**.

The new thiol-derivative **117** of the Abiko-Masamune auxiliary can be acylated using propionyl or acetyl chloride in the presence of pyridine, to give the chiral propionyl **131** or acetyl **128** thiolesters used as substrates for the study of propionate or acetate boron-mediated aldol reactions (**scheme 39**).



Scheme 39: Acylation of the chiral auxiliary **117**. Reagents and Conditions: a) **129**, py, CH_2Cl_2, 18 h, RT (91%). b) **130**, py, CH_2Cl_2, 18 h, RT (93%).

The X-ray crystal structure[91] of **131** (**figure 11**), proved the overall net retention of stereochemistry from (1*S*,2*R*)-norephedrine of the synthetic sequence described in **scheme 37**.



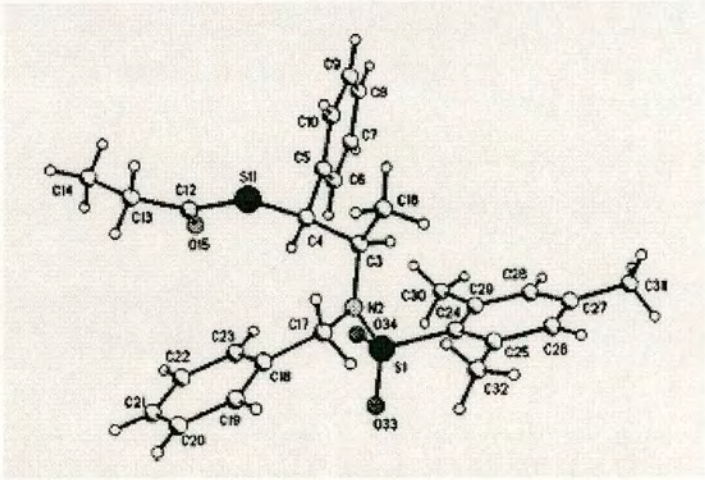
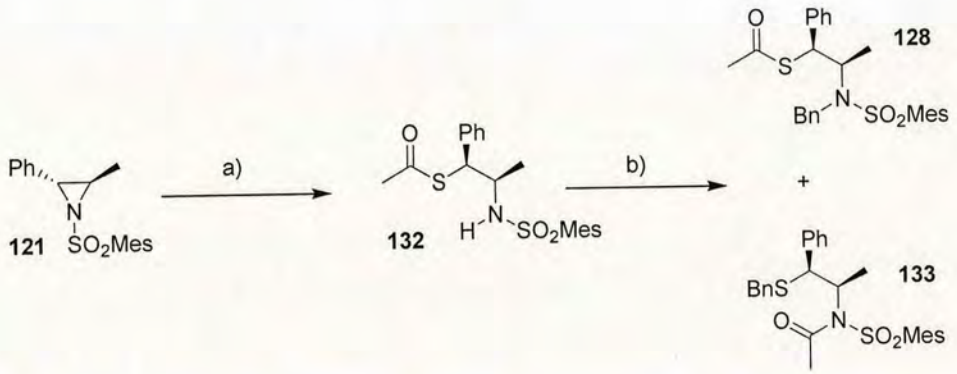


Figure 11: X-ray crystal structure of propionate derivative **131**.[91]

An alternative strategy to generate acetyl thiolester **128** in just two steps was also investigated. Opening of aziridine **121** with thiolacetic acid in the presence of catalytic PBu_3, as previously described in **scheme 33**, gave thiolester **132** in good yield.[93-95] However, use of the optimised conditions found to avoid benzoate migration (**table 1**) failed to generate the desired product **128**. Treatment of **132** under these conditions (**scheme 40**) allowed acetyl group migration to a very high extent probably due to the lesser steric hindrance of the acetyl group compared to its benzoyl counterpart.

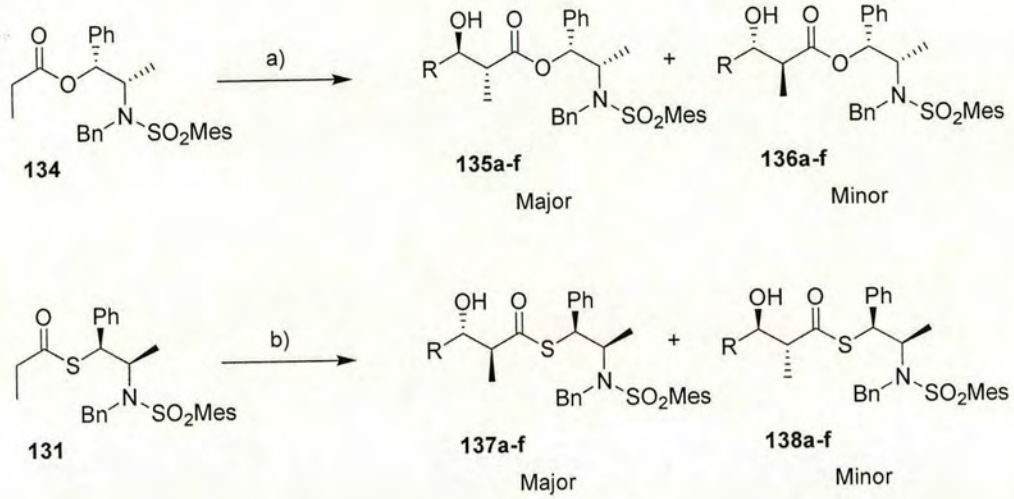


Scheme 40: Failed strategy towards the synthesis of acetyl thiolester **128**. Reagents and conditions: a) CH_3COSH, PBu_3 (10 mol%), MeCN/H_2O, 18 h, RT (68%). d) NaH, BnBr, DMF, 18 h, RT (94% of **133**, 4% of **128**).

2.2 *ANTI* PROPIONATE ALDOL REACTIONS

2.2.1 Synthesis of *Anti* Propionate Aldols.

Previous studies within the Hulme group[91] proved that the new sulfur derivative **117** of the Abiko-Masamune auxiliary could be effectively used for the *anti*-selective boron-mediated propionate aldol reaction, achieving high yields and diastereoselectivities with a range of aldehydes, when the optimised conditions developed by Abiko[33-34] were used. Enolisation of the chiral propionyl thiolester **131** with dicyclohexylboron triflate and triethylamine at -78°C prior to addition of the aldehyde, produced *anti* aldol adducts in yields and diastereoselectivities comparable to those achieved with the Abiko-Masamune auxiliary (**table 2**).[33,91]



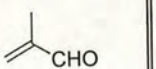
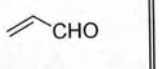
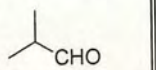
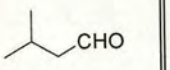
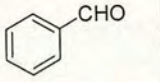
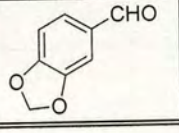
		MASAMUNE	SULFUR DERIVATIVE
Aldehyde		Yield (%) / ds (*anti* : *anti*) (**135**:**136**)	Yield (%) / ds (*anti* : *anti*) (**137**:**138**)[c]
a		97 (96 : 4)[33]	90 (92 : 8)[91]
b		79 (98 : 2)[91]	92 (93 : 7)[91]
c		95 (98 : 2)[33]	94 (92 : 8)[92]
d		------	94 (94 : 6)[91]
e		93 (95 : 5)[33]	85 (91 : 9)[91]
f		------	91 (97 :3)[91]

Table 2: Synthesis of *anti* propionate aldols with the Abiko-Masamune auxiliary and its sulfur derivative. Reagents and conditions: a) c-Hex_2BOTf (2.0 eq.), Et_3N (2.4 eq.), CH_2Cl_2, -78 °C for 2 h; then RCHO (1.2 eq.), -78 °C for 1 h, 0 °C for 1 h (*anti*:*syn* > 98:2). b) c-Hex_2BOTf (2.0 eq.), Et_3N (3.0 eq.), CH_2Cl_2, -78 °C for 2 h; then RCHO (3.0 eq.), -78 °C for 2 h, 0 °C for 1 h (*anti*:*syn* > 98:2). [c] by NMR and HPLC of diastereomeric mixture.

As shown above *anti*-aldol adducts were produced with a wide range of aldehydes (vinyl, alkyl and aromatic), with only a minor erosion of facial selectivity when switching from the ester to the thiolester.[92] As with the classic auxiliary,[30-34] the minor diastereoisomer has been assigned as the other *anti* isomer as discussed in the following section.

2.2.2 Assignment of Relative Stereochemistry

The relative stereochemistry of the four possible diastereoisomers was assigned on the basis of the coupling constant between C2 and C3 protons in the aldol adducts generated with a range of aldehydes. This coupling constant is smaller in *syn*-aldol adducts (typically 3-4 Hz) than in *anti*-aldol products (between 7-8 Hz) (**figure 12**).[96]

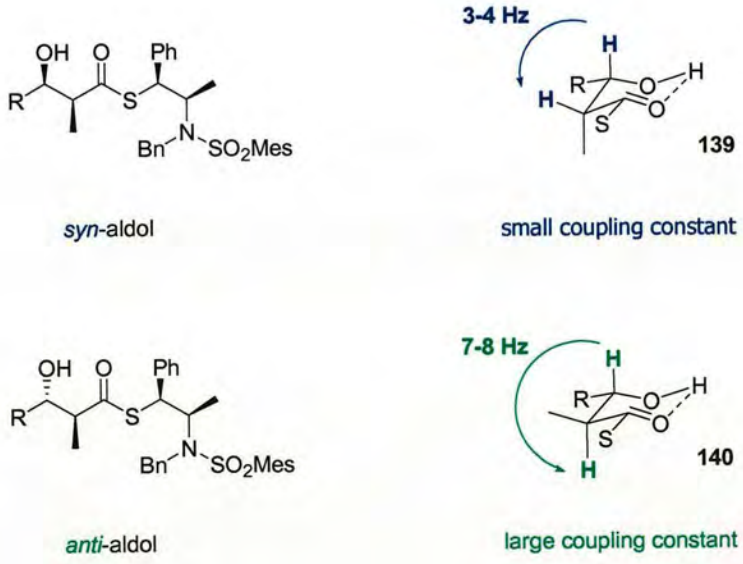
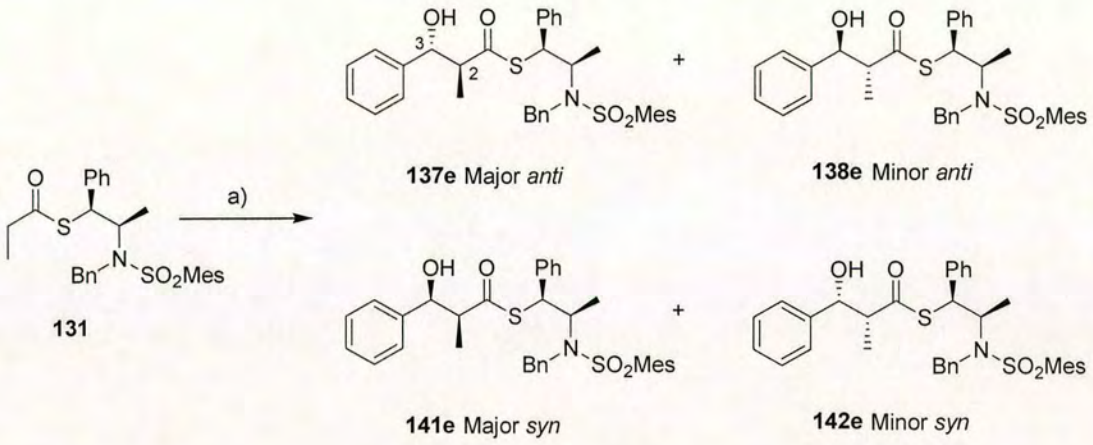


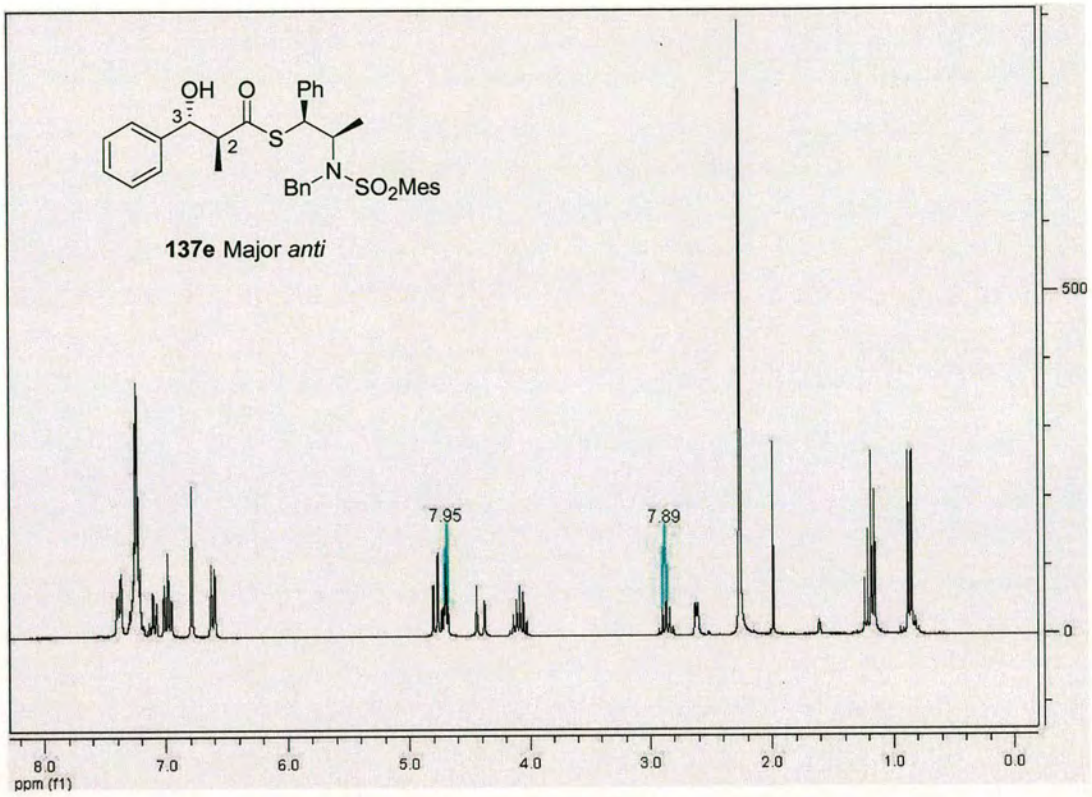
Figure 12: Coupling constants in *syn*- and *anti*-aldols.

For example, NMR examination of the four diastereoisomers generated from benzaldehyde (**scheme 41**) allowed assignment of *syn* and *anti* stereochemistry of the aldol adducts.



Scheme 41: Four possible diastereoisomers from benzaldehyde. Reagents and conditions: a) Bu_2BOTf (2.0 eq.), $^iPr_2NEt$ (3.0 eq.), CH_2Cl_2, -78 °C for 2 h; then benzaldehyde (3.0 eq.), -78 °C for 1.5 h, 0 °C for 1 h (88%, *anti*:*syn* = 98:2, *anti*:*anti* = 82:18).

The *anti* stereochemistry of aldol adducts **137e** and **138e** was assigned by NMR analysis. The coupling constant between C2 and C3 protons was found to be 7.9 Hz in the aldol adduct **137e** (**figure 13**) and 8.3 Hz in aldol adduct **138e** (**figure 14**). Both are within the typical range for *anti*-vicinal protons. Similarly, the *syn* stereochemistry of aldol adducts **141e** and **142e** was assigned on the basis of their coupling constants, which were found to be 5.4 Hz in aldol adduct **141e** (**figure 15**) and 3.7 Hz in aldol adduct **142e** (**figure 16**).



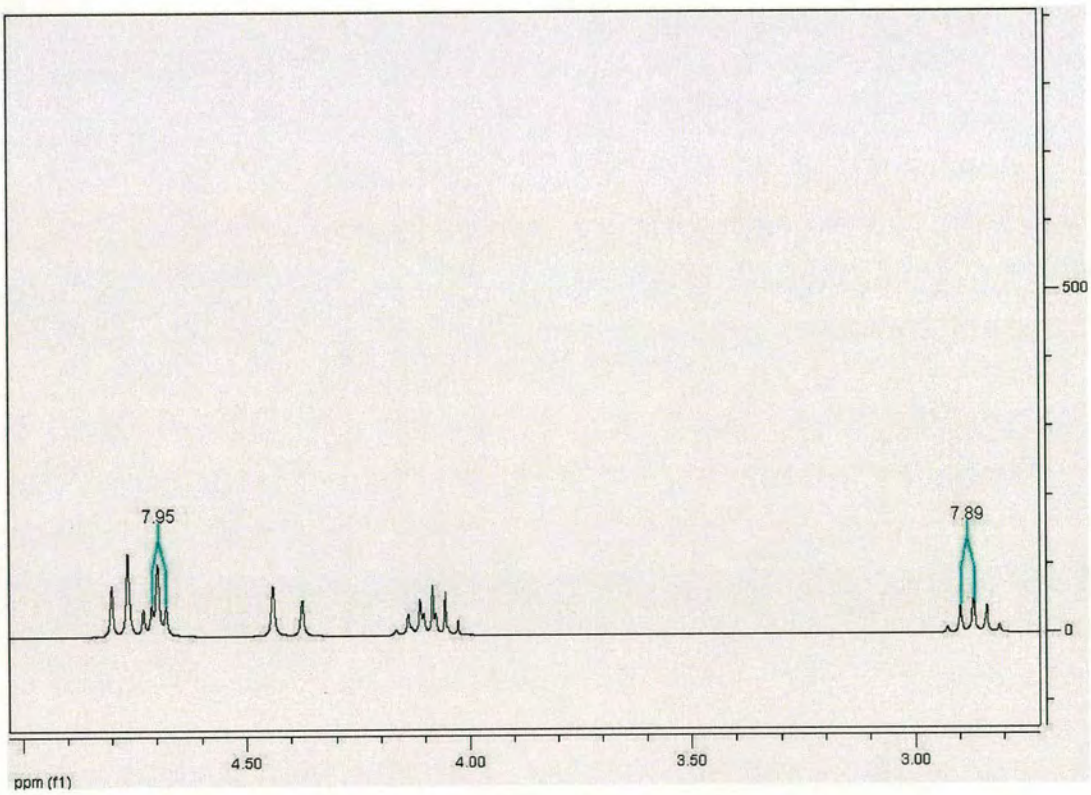
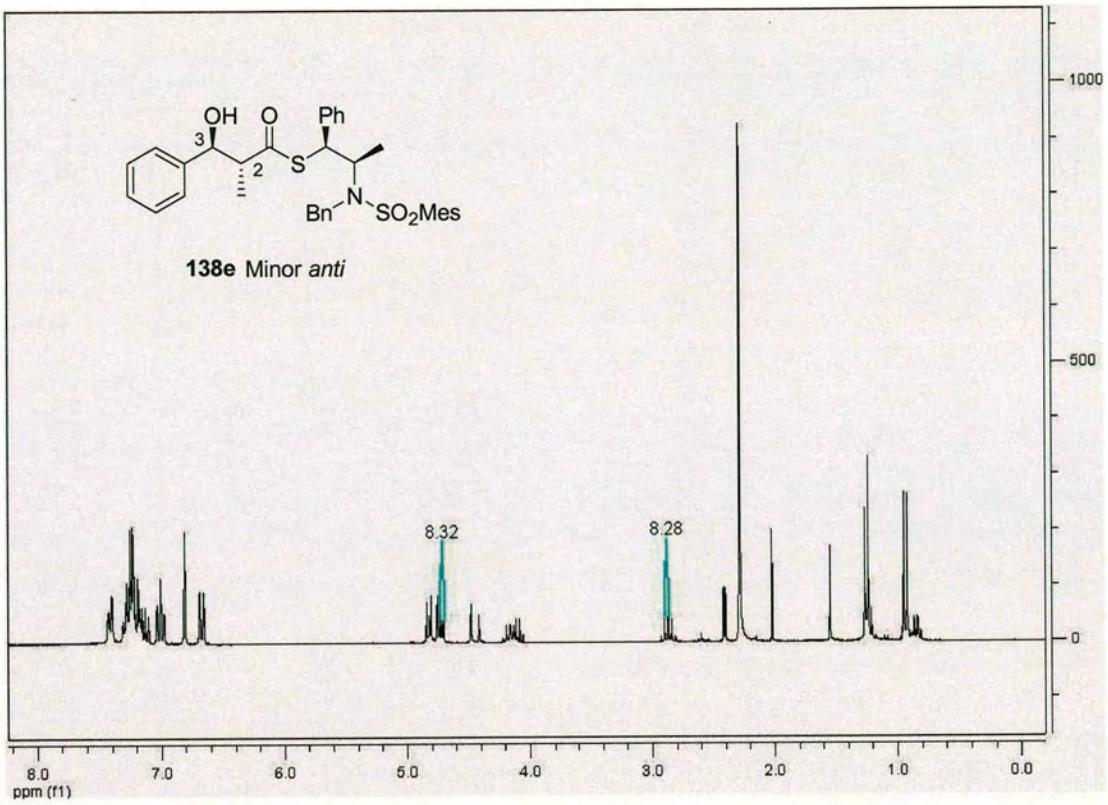


Figure 13: The NMR of major *anti*-aldol adduct **137e** and its expansion, showing the coupling constant between C2 and C3 protons.



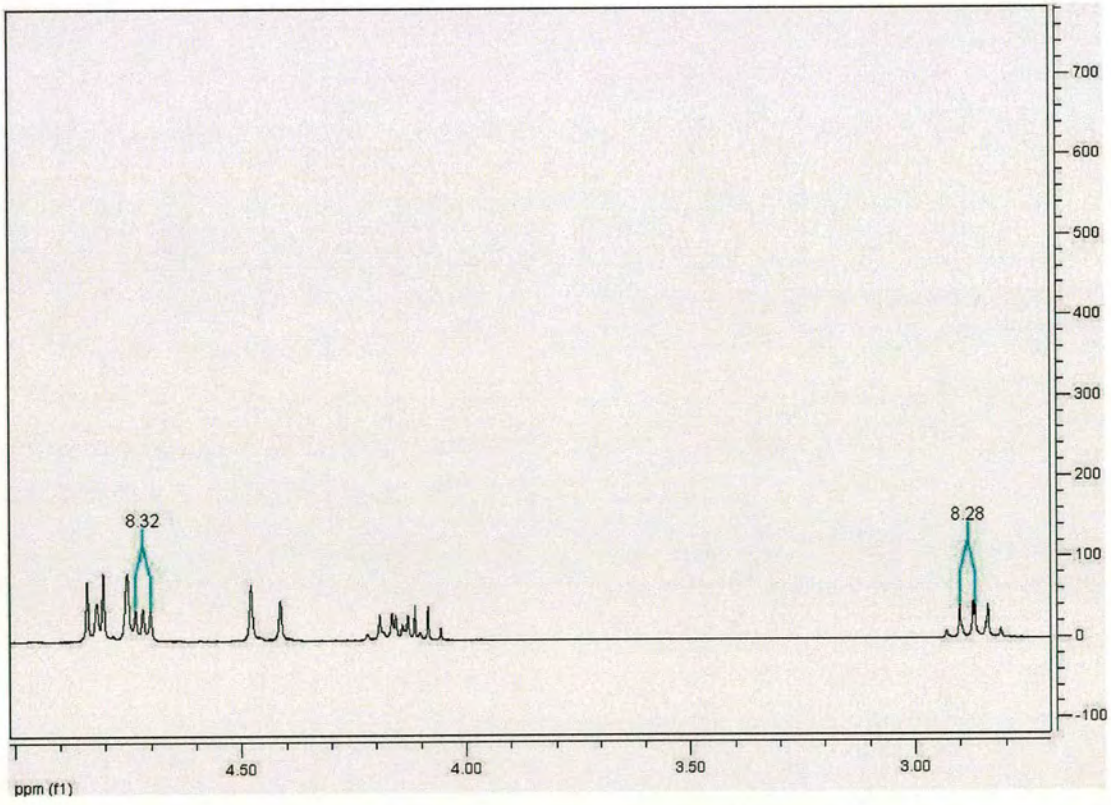
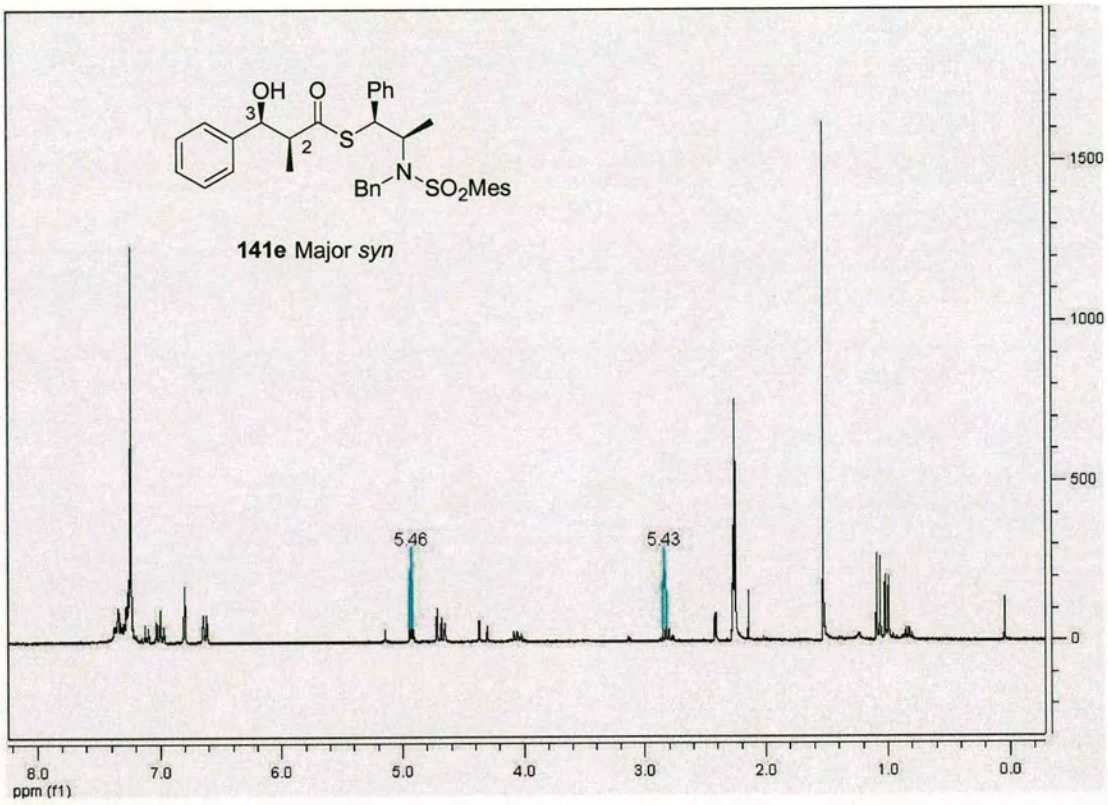


Figure 14: The NMR of minor *anti*-aldol adduct **138e** and its expansion, showing the coupling constant between C2 and C3 protons.



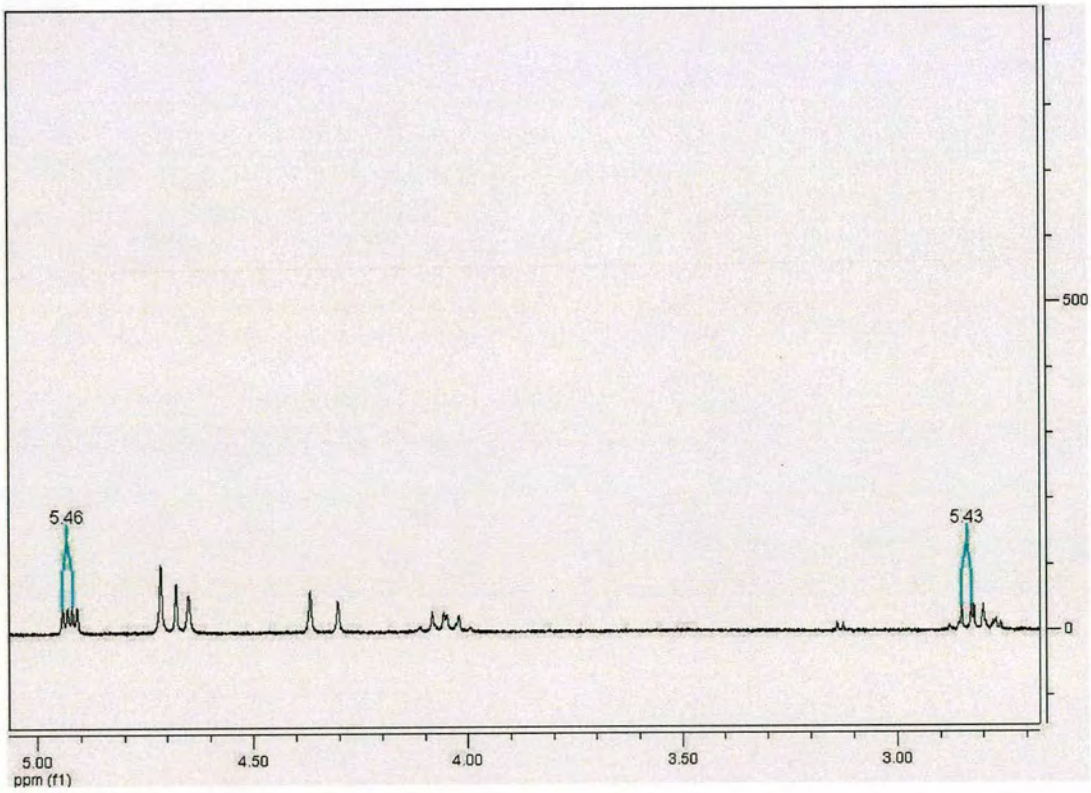
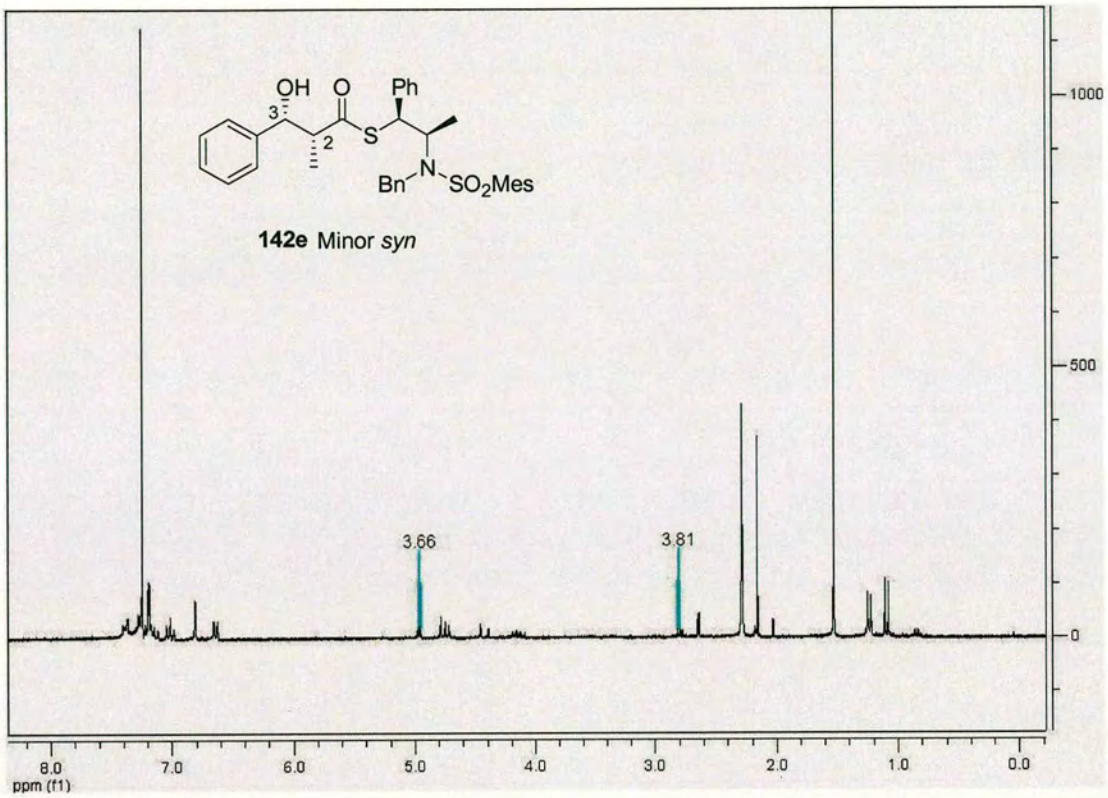


Figure 15: The NMR of major *syn*-aldol adduct **141e** and its expansion, showing the coupling constant between C2 and C3 protons.



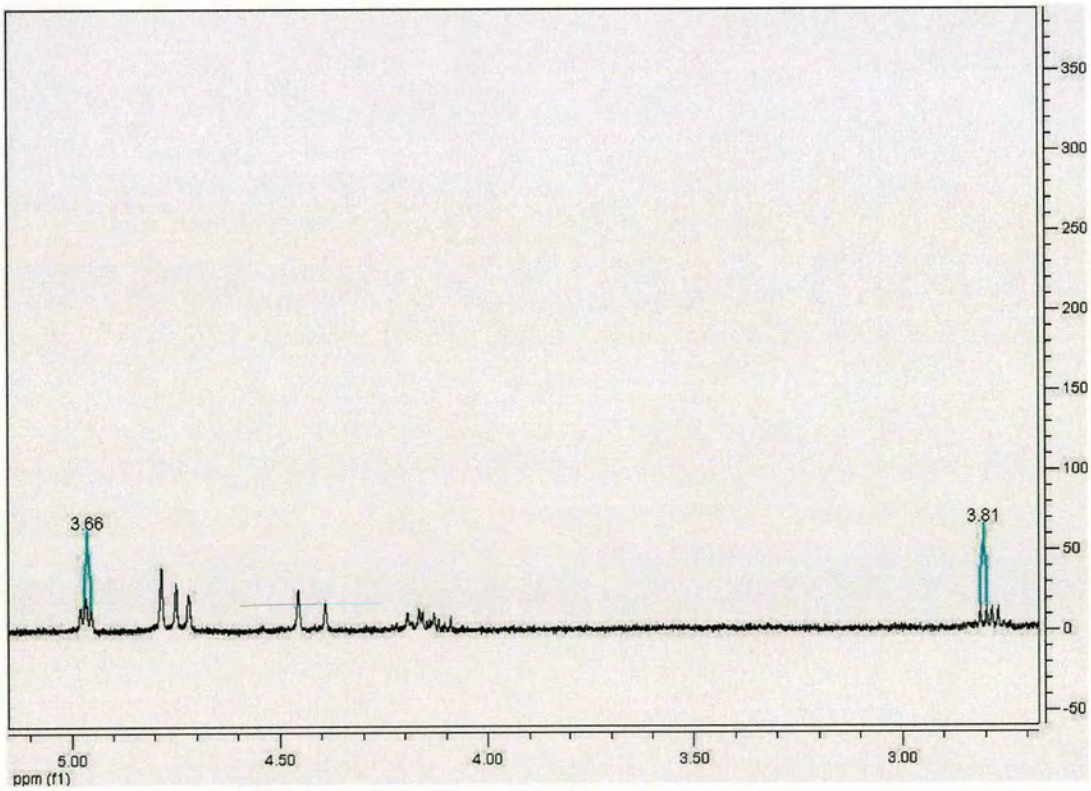
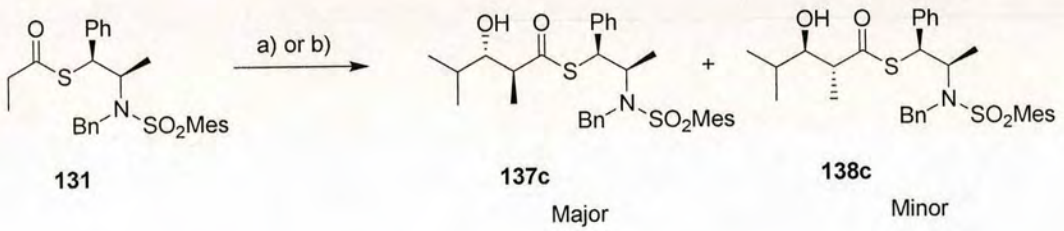


Figure 16: The NMR of minor *syn*-aldol adduct **142e** and its expansion, showing the coupling constant between C2 and C3 protons.

2.2.3 Proof of Absolute Stereochemistry

The absolute stereochemistry was assigned based on optical rotations values calculated from different derivatives of the aldol adducts, and their comparison with known values in the literature.

Aldol reaction between thiolester **131** and isobutyraldehyde was carried out under the two sets of optimised conditions developed by Abiko for *anti*- or *syn*-selective boron-mediated aldol reactions of esters. Surprisingly both sets of conditions afforded *anti*-aldol products **137c** and **138c**.

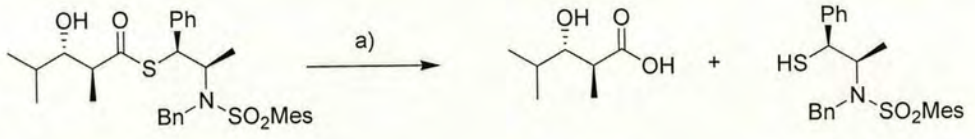


131 **137c** Major **138c** Minor

Scheme 42: Synthesis of *anti*-aldol adducts from isobutyraldehyde. Reagents and conditions: a) c-Hex_2BOTf (2.2 eq.), Et_3N (2.4 eq.), CH_2Cl_2, -78 °C for 2 h; then isobutyraldehyde (2.5 eq.), -78 °C for 2 h, 0 °C for 1 h (94%, *anti*:*syn* > 99:1, *anti*:*anti* = 92:8). b) Bu_2BOTf (2.0 eq.), $^iPr_2NEt$ (3.0 eq.), CH_2Cl_2, -78 °C for 2 h; then isobutyraldehyde (3.0 eq.), -78 °C for 1.5 h, 0 °C for 1 h (94%, *anti*:*syn* > 99:1, *anti*:*anti* = 81:19).

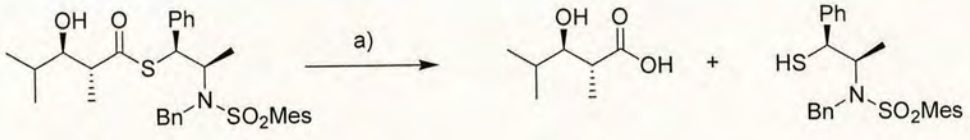
Assignment of the relative *anti*-stereochemistry was carried out by proton NMR analysis. Coupling constant between the C2 and C3 protons was found to be 6.9 Hz in aldol adduct **137c** and 7.1 Hz in **138c**. Both are typical values of coupling constants between vicinal *anti* protons in aldol substrates.[96]

The absolute stereochemistry of both *anti* isomers was assigned by measurement of optical rotation values from acid derivatives **143** and **144** (obtained by hydrolysis of **137c** and **138c**), and their comparison with the literature (**scheme 43**).[96-98]



137c Major **143** **117**

$[\alpha]_D$ = + 14.3 / Lit.[97] $[\alpha]_D$ = + 14.1

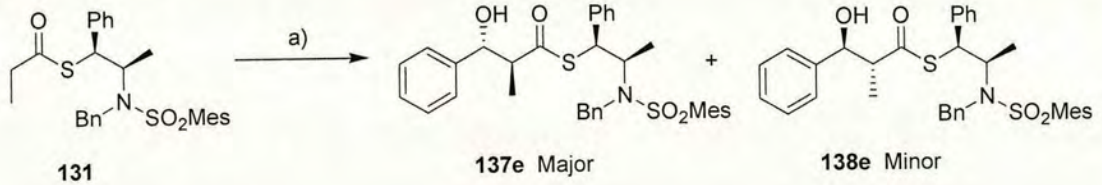


138c Minor **144** **117**

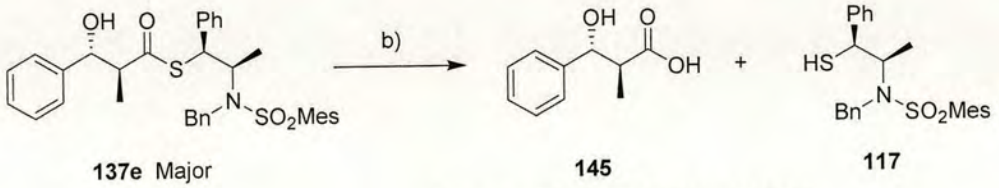
$[\alpha]_D$ = - 16.0 / Lit.[98] $[\alpha]_D$ = - 15.3

Scheme 43: Hydrolysis of *anti*-aldols and proof of absolute stereochemistry by optical rotation.[96-98] Reagents and conditions: a) LiOH (3.0 eq.), THF/H_2O (2:1), RT, 30 min (88% of **143**; **117** recovered in 99%) (86% of **144**; **117** recovered in 88%).

Following a similar procedure to that described in **scheme 42**, *anti*-aldol adducts **137e** and **138e** were generated from benzaldehyde. Major product **137e** was then hydrolysed to give acid **145** (**scheme 44**).



131 **137e** Major **138e** Minor



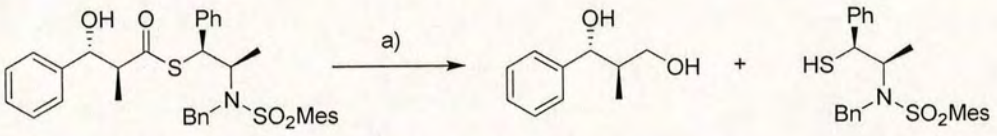
137e Major **145** **117**

$[\alpha]_D$ = + 17.5 / Lit.[97] $[\alpha]_D$ = + 17.8

Scheme 44: Synthesis and hydrolysis of *anti*-aldols. Proof of absolute stereochemistry by optical rotation.[97] Reagents and conditions: a) Bu_2BOTf (2.0 eq.), $^iPr_2NEt$ (3.0 eq.), CH_2Cl_2, -78 °C for 2 h; then benzaldehyde (3.0 eq.), -78 °C for 1.5 h, 0 °C for 1 h (88%, *anti*:*syn* > 99:1, *anti*:*anti* = 82:18). b) LiOH (20 eq.), THF/H_2O (2:1), RT, 20 min (98% of **145**, 89% of **117**).

The $[\alpha]_D$ obtained for acid **145** was in good agreement with the literature value,[97] proving consistency in the stereochemical outcome of the aldol reaction (**scheme 44**). It also demonstrated achievement of the same absolute stereochemistry with the thiol auxiliary **117** with that reported with the Abiko-Masamune auxiliary.[30-34]

Major aldol adduct **137e** was also converted into its diol derivative **146** by reduction with $NaBH_4$. The optical rotation of **146** was again in good agreement with the literature and the ester precedent (**scheme 45**).[99,100]



137e Major **146** **117**

$[\alpha]_D$ = + 32.0 / Lit.[99] $[\alpha]_D$ = + 35.2

Scheme 45: Synthesis and optical rotation value[99,100] of **146**. Reagents and conditions: a) $NaBH_4$ (10 eq.), THF(aq.), RT, 14 h (99% of **146**, 83% of **117**).

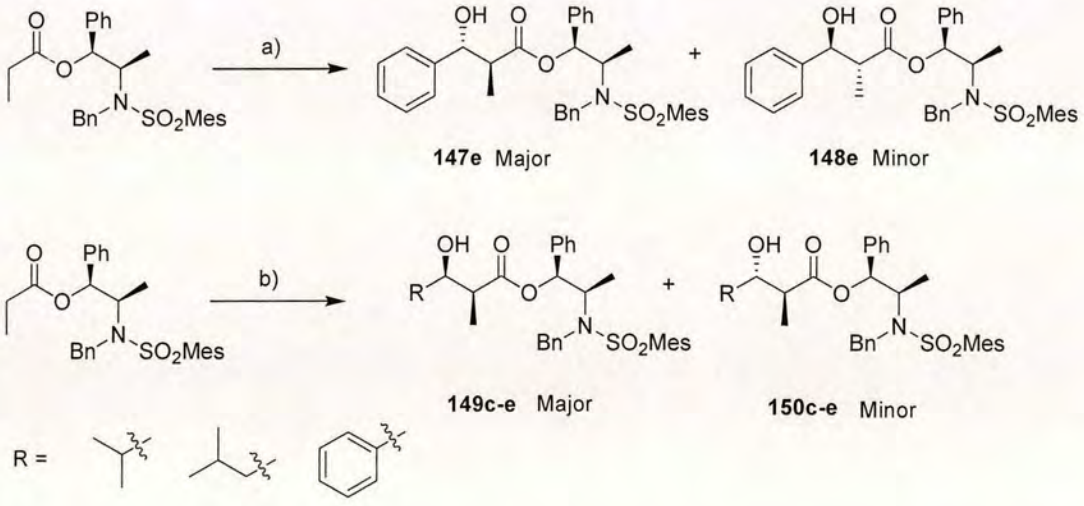
Having taken into account these results and that *syn* aldol adducts were generally present in less than 2% under all the conditions investigated, assignment of the absolute stereochemistry for the *syn* aldol adducts was made on the basis of the Abiko-Masamune precedent.[30-34]

2.3 *SYN*-PROPIONATE ALDOL REACTIONS

2.3.1 Attempted Synthesis of *Syn*-Propionate Aldols Using the Abiko-Masamune Optimised Conditions

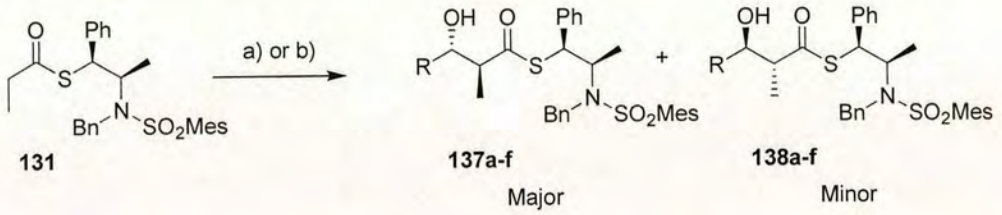
Studies reported by Abiko and Masamune have shown that through the appropriate choice of the enolisation reagents either *anti*- or *syn*-aldol adducts can be obtained. As described in **table 2** the formation of *anti* aldols is controlled by the presence of bulky ligands on the boron (c-Hex_2BOTf) and the addition of a non-bulky base (Et_3N) to form the *E*-enolate. In contrast, the combination of small ligands on the boron (Bu_2BOTf) and a larger base ($^iPr_2NEt$) leads to the formation of the *Z*-enolate, and therefore the synthesis of *syn*-aldol adducts.[33,34]

Although both *anti*- and *syn*-selective aldol reaction conditions have been reported, only the *anti*-selective aldol reaction of esters has been widely used in synthesis, with no known examples of *syn*-selective propionate aldol reactions of the Abiko-Masamune auxiliary in natural product synthesis. Thus, in our preliminary studies we decided to investigate both set of conditions with the Abiko-Masamune auxiliary to then compare these results with the sulfur analogue (**scheme 46**).



Scheme 46: Synthesis of *anti* and *syn* Masamune aldols using Abiko's optimised conditions. Reagents and conditions: a) c-Hex_2BOTf (2.2 eq.), Et_3N (2.4 eq.), CH_2Cl_2, -78 °C for 1.5 h; then PhCHO (1.5 eq.), -78 °C for 2 h, 0 °C for 1.5 h (*anti*:*anti* = 98:2). b) Bu_2BOTf (2.0 eq.), $^iPr_2NEt$ (3.0 eq.), CH_2Cl_2, -78 °C for 2 h; then RCHO (1.5 eq.), -78 °C for 1 h, 0 °C for 1 h (isobutyraldehyde, *syn*:*anti* = 94:6; isovaleraldehyde, 83:17; benzaldehyde, 89:11).

Unfortunately, use of the optimised conditions to give *syn*-aldol adducts reported by Abiko,[33,34] failed to produce *syn*-aldols when the sulfur derivative of the Abiko-Masamune auxiliary was used. Treatment of thiolester **131** with Bu_2BOTf and $^iPr_2NEt$ gave only *anti*-aldol adducts in high yield with a range of aldehydes. In all cases an erosion of the facial selectivity was observed compared to the selectivities achieved when the *anti* conditions were used (**table 3**).



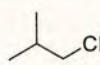
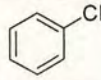
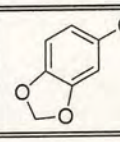
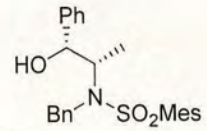
		SYN CONDITIONS[a]	*ANTI* CONDITIONS[b]
Aldehyde		Yield (%) / ds (*anti* : *anti*)[c]	Yield (%) / ds (*anti* : *anti*)[c]
a		87 (79 : 21)	90 (92 : 8)
b		89 (76 : 24)	92 (93 : 7)
c		94 (81 : 19)	94 (92 : 8)
d		84 (77 : 23)	94 (94 : 6)
e		88 (82 : 18)	85 (91 : 9)
f		80 (85 : 15)	91 (97 :3)

Table 3: Synthesis of *anti* propionate aldols using the *syn* conditions reported by Abiko.[33,34] Reagents and conditions: a) Bu_2BOTf (2.0 eq.), $^iPr_2NEt$ (3.0 eq.), CH_2Cl_2, -78 °C for 2 h; then RCHO (3.0 eq.), -78 °C for 1.5 h, 0 °C for 1 h (*anti*:*syn* > 99:1). b) c-Hex_2BOTf (2.0 eq.), Et_3N (3.0 eq.), CH_2Cl_2, -78 °C for 2 h; then RCHO (3.0 eq.), -78 °C for 2 h, 0 °C for 1 h (*anti*:*syn* > 98:2). [c] by NMR and HPLC of diastereomeric mixture.

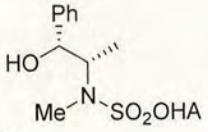
Although auxiliary **151** (derived from norephedrine) led to the formation of *syn*-aldol adducts when Bu_2BOTf and $^iPr_2NEt$ were used as the enolisation reagents in the boron-mediated aldol reaction of Masamune esters, the diastereoselectivities *syn* to *anti* achieved (*e.g.* 87:13 *syn*:*anti* with isobutyraldehyde) were not comparable to those *anti* to *syn* obtained with c-Hex_2BOTf and Et_3N (*e.g.* > 98:2 *anti*:*syn* with isobutyraldehyde). Thus, Abiko and co-workers developed a different auxiliary **152** (derived from ephedrine) (**figure 17**) for the *syn*-selective propionate aldol reaction with esters, to achieve higher selectivities (*e.g.* > 95:5 with isobutyraldehyde).[33] While the sulfur derivative of **151** and not that from **152** was used in our studies, the absence of *syn*-aldol adducts observed cannot be attributed to the selection of the wrong auxiliary, as high conversion to *syn* aldol adducts was possible in the case of the Abiko-Masamune auxiliary even when the non-optimum reagent **151** was used.[33]

Mes = 2,4,6-trimethylphenyl.

OHA = 1,2,3,4,6,7,8,9-octahydroanthracenyl.



151



152

Figure 17: Optimum reagents for *anti* and *syn* boron-mediated propionate aldol reactions with esters.[33,34]

At this point several attempts to try to synthesise *syn*-aldol adducts were investigated.

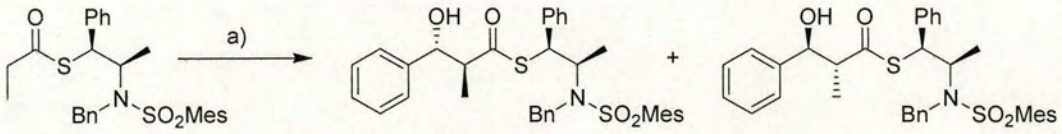
2.3.2 Investigation of the Effects of Different Bases and Triflates on Enolisation

The effects of varying the base and the leaving groups on the boron reagents with respect to the stereochemical outcome of the aldol reaction have been widely investigated in the literature. It is known that the combination of small ligands on boron (*e.g.* n-butyl), a good leaving group (*e.g.* triflate) and a bulky amine base (*e.g.* $^{i}Pr_2NEt$) usually leads to the formation of *syn* aldols by *Z*-selective enolisation.[6-13] This precedent is in agreement with the conditions reported by Abiko to generate *syn*-aldol adducts,[33] in which the variation of base and triflate used has been shown to have a great effect on the reaction outcome in the case of the Masamune auxiliary-mediated reaction. Thus, this formed the focus of our initial investigation (**table 4**).

Although different combinations of triflates and bases were carried out in the first place, none of the conditions studied led to the formation of *syn*-aldols. In all cases, *anti* products were obtained to a very high extent (*anti*:*syn* > 91:9) (**table 4**).

Switching from large ligands on the boron (c-Hex_2BOTf) to smaller ones (Bu_2BOTf, 9-BBNOTf, Et_2BOTf) seems to lead to a decrease in facial selectivity (from 90:10 to 80:20 *anti*:*anti* selectivity; entry 2 *vs* entries 4, 6 and 8); however, it fails to have a significant influence on the *syn*:*anti* selectivity. While c-Hex_2BOTf and Bu_2BOTf (entries 2 and 4) produce almost exclusively *anti* products (99:1), smaller ligands on the boron (9-BBNOTf and Et_2BOTf; entries 6 and 8) seem to slightly increase the formation of *syn*-aldol adducts (92:8, 91:9 respectively) (**table 4**).

Interestingly, in most cases the use of Et_3N failed to induce the formation of aldol adducts (entries 3, 5 and 7). Only the combination of Et_3N with c-Hex_2BOTf (entry 1) allowed the reaction to take place. Similar results have been reported in the literature.[33] Boron-mediated aldol reactions of benzyl propionate did not occur when Et_2BOTf and Et_3N were used; in contrast, Et_2BOTf and $^{i}Pr_2NEt$ produced aldol adducts in high yield (96%). The combination of Bu_2BOTf and Et_3N generated aldols in poor yield (10%); while Bu_2BOTf and $^{i}Pr_2NEt$ gave a 97% yield. Finally, Et_3N combined with c-Hex_2BOTf generated aldol adducts in 92% yield.[33]



131 **137e** Major **138e** Minor

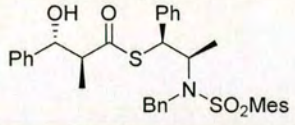
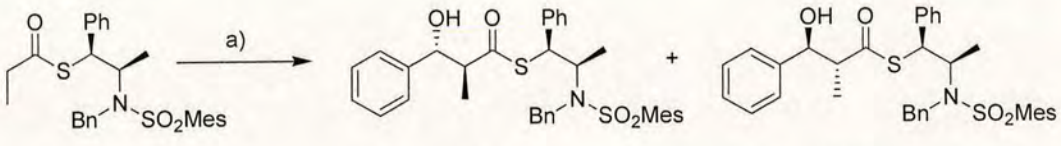
		
Entry	Triflate / Base	Yield (%) / ds (*anti* : *anti*) // ds (*anti* : *syn*)[b]
1	$(^{c}Hex)_2BOTf$ / Et_3N	85 (91 : 9) // (99 : 1)
2	$(^{c}Hex)_2BOTf$ / $^{i}Pr_2NEt$	86 (90 : 10) // (99 : 1)
3	Bu_2BOTf / Et_3N	no reaction
4	Bu_2BOTf / $^{i}Pr_2NEt$	88 (82 : 18) // (99 : 1)
5	9-BBN-OTf / Et_3N	no reaction
6	9-BBN-OTf / $^{i}Pr_2NEt$	81 (82 : 18) // (92 : 8)
7	Et_2BOTf / Et_3N	no reaction
8	Et_2BOTf / $^{i}Pr_2NEt$	84 (80 : 20) // (91 : 9)

Table 4: Synthesis of *anti* aldols with different triflates and bases. Reagents and conditions: a) Triflate, Base, CH_2Cl_2, -78 °C; then PhCHO, from -78 °C to 0 °C. [b] by NMR and HPLC of diastereomeric mixture.

2.3.3 Investigation of the Effects of Different Leaving Groups on Boron and Solvents on Enolisation

It is known that the use of bulky ligands on boron (*e.g.* cyclohexyl), a poor leaving group (*e.g.* chloride) and a small amine base (*e.g.* triethylamine) usually promotes *E*-enolate formation.[6-13] When **131** was subjected to these conditions (entries 1 and 3), the experimental results confirmed the predicted outcome of the reaction as *anti*-products were recovered in high yield and with excellent diastereoselectivities. Dicyclohexylboron chloride and Et_3N gave *anti*-aldol adducts in 92% yield, 90:10 *anti*:*anti* diasterofacial selectivity and 97:3 *anti*:*syn* diastereoselectivity (entry 1, **table 5**). In contrast, when $^iPr_2NEt$ was used as the base the reaction did not take place (entry 2, **table 5**).



131 **137e** Major **138e** Minor

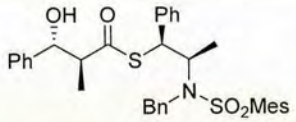
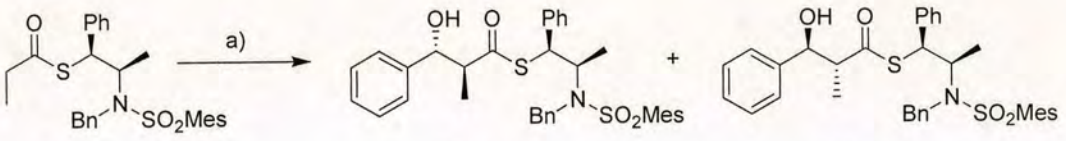
		
Entry	Base / Solvent	Yield (%) / ds (*anti* : *anti*) // ds (*anti* : *syn*)[b]
1	Et_3N / CH_2Cl_2	92 (90 : 10) // (97 : 3)
2	$^iPr_2NEt$ / CH_2Cl_2	no reaction
3	Et_3N / Ether	82 (85 : 15) // (98 : 2)

Table 5: Synthesis of *anti*-aldol adducts with c-Hex_2BCl. Reagents and conditions: a) c-Hex_2BCl, Base, Solvent, -78 °C; then PhCHO, from -78 °C to 0 °C. [b] by NMR and HPLC of diastereomeric mixture.

The experimental results described in **table 5** also proved the comparatively minor influence of the solvent on the stereochemical outcome of the aldol reaction. Use of either CH_2Cl_2 or ether did not appear to have a major impact on the stereoselectivity of the reaction, and only a slight erosion of the facial selectivity was observed when ether was used (entry 1 *c.f.* 3).

2.3.4 Investigation of the Effects of Enolisation Temperature

The effect of the temperature in the enolisation process was also investigated. Abiko has reported isomerisation of the *E*-enolate (kinetic) to the *Z*-enolate (thermodynamic) by heating. An aldol reaction performed on EtCOOBn at -95 °C using c-Hex_2BOTf/Et_3N afforded the *anti*-aldol product in 97:3 ratio.[33] When the enolate solution was warmed to 0 °C before addition of aldehyde, the *syn*-aldol adduct was obtained as a major product (*anti*:*syn* = 33:67 after 30 min and 10:90 after 1 h). In our case, when the enolisation was carried out at 0 °C, with either c-Hex_2BOTf/Et_3N or $Bu_2BOTf/^iPr_2NEt$, no significant *Z*-enolate formation was observed compared with the results obtained at -78 °C. However, some erosion of selectivity occurred with Bu_2BOTf and $^iPr_2NEt$ when the enolisation was performed at room temperature (*anti*:*syn* from 99:1 at -78 °C to 87:13 at RT) (**table 6**).



131 **137e** Major **138e** Minor

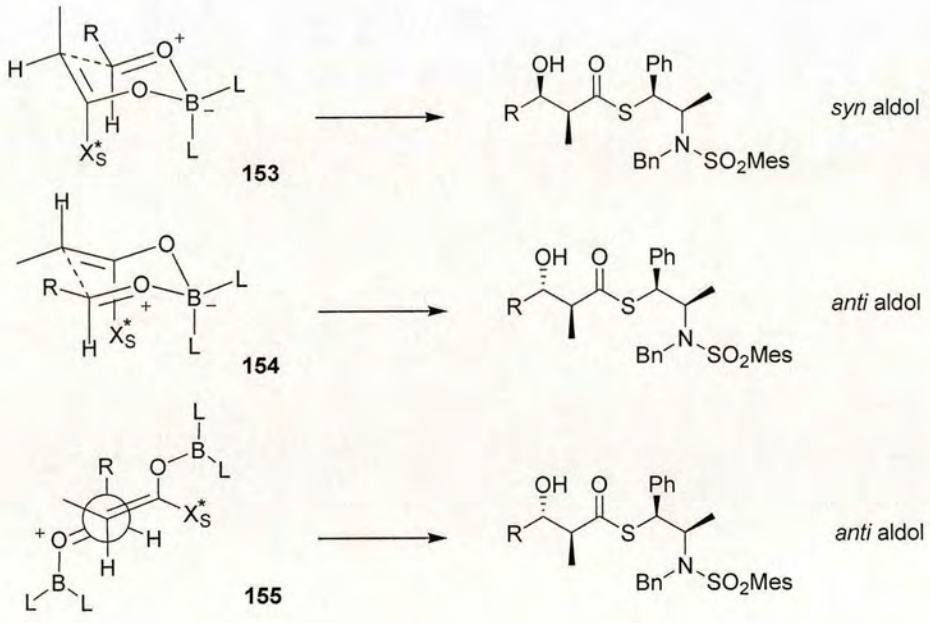
	$(^cHex)_2BOTf$ / Et_3N	Bu_2BOTf / $^iPr_2NEt$
Temperature	Yield (%) / ds (*anti* : *anti*) // ds (*anti* : *syn*)[b]	Yield (%) / ds (*anti* : *anti*) // ds (*anti* : *syn*)[b]
-78 °C	85 (91 : 9) // (99 : 1)[91]	88 (82 : 18) // (99 : 1)
0 °C	82 (82 : 18) // (95 : 5)	80 (81 : 19) // (94 : 6)
RT	71 (49 : 51) // (96 : 4)	82 (52 : 48) // (87 : 13)

Table 6: Propionate aldol enolisations carried out at different temperatures. Reagents and conditions: a) Triflate/Base in CH_2Cl_2, at -78 °C (2 h), 0 °C (1 h) or room temperature (1 h); then PhCHO. [b] by NMR and HPLC of diastereomeric mixture.

Although changes in the temperature did not afford extensive formation of the *Z*-enolate, it did have an effect on the facial selectivity. Significant loss of diastereofacial selectivity was observed at higher enolisation temperatures (*anti*:*anti* from 91:9 at -78 °C to around 50:50 at RT) (**table 6**).

2.3.5 Investigation of the Number of Equivalents of Lewis Acid

Assuming that the reaction takes place through a Zimmerman-Traxler transition state, generation of *Z*-enolates would lead to the formation of *syn*-aldol adducts, while the production of *E*-enolates would afford *anti*-aldol products (**scheme 47**). However, as reported with Evans' oxazolidinones (**scheme 23**),[68-70] in the presence of an excess of Lewis acid (*e.g.* triflate) the aldol reaction could proceed through an open transition state **155**; leading to a change in the stereochemical outcome of the reaction (**scheme 47**).



Scheme 47: Closed and open transition states leading to *syn* or *anti* aldol adducts.

For this reason, the influence of the number of equivalents of triflate used in the aldol reaction was investigated. When only 1.0 equivalent of Bu_2BOTf was used for the aldol reaction with isobutyraldehyde in the presence of 1.5 equivalents of $^iPr_2NEt$ at -78 °C, *anti*-aldol products were obtained in 46% yield and 80:20 *anti*:*anti* diastereofacial selectivity, while none of the *syn*-products were detected. These results are similar to those achieved when 2.0 equivalents of Bu_2BOTf were used in the presence of 3.0 equivalents of base under the same reaction times and temperatures (88%, *anti*:*anti* = 82:18), demonstrating that when the triflate:base ratio is maintained, but the overall number of equivalents of triflate is increased, only the extent of the conversion and not the stereochemistry was affected. In contrast, Heathcock[68] has reported a reversal of stereochemistry with Evans' oxazolidinones when an excess of triflate and no significant changes in the triflate:base ratio were investigated. Treatment of Evans' auxiliary propionate derivative with 1.1 equivalents of Bu_2BOTf in the presence of 1.3 equivalents of $^iPr_2NEt$ afforded excellent *syn*:*anti* selectivity (> 98:2). However, use of an excess of Lewis acid promoted a reversal of the stereochemical outcome of the reaction, affording *anti* aldol adducts in high selectivities (*syn*:*anti* = 23:77 with 1.5 eq. of Bu_2BOTf and 2.0 eq. of $^iPr_2NEt$; *syn*:*anti* = 5:95 with 2.0 eq. of Bu_2BOTf and 2.2 eq. of $^iPr_2NEt$).[68]

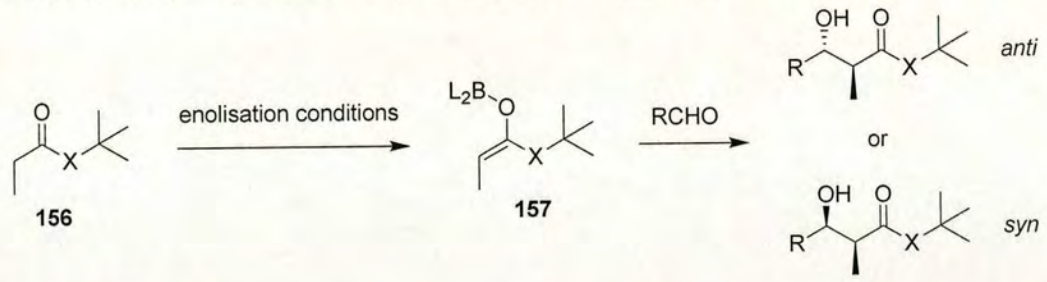
Changes in the enolisation time (45min-2.5 h), reaction time (3-8 h) and number of equivalents of base (1.5-4.0 eq.) and aldehyde (1.2-4.0 eq.) were also shown to only affect the yield and not the diastereoselectivity of the reaction.

2.4 RATIONALISATION STUDIES

2.4.1 Literature Precedent

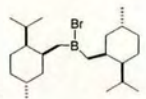
While the Masamune auxiliary appears to allow access to both the *E*-enolate (c-Hex_2BOTf, Et_3N, -78 °C, 2 h, then isobutyraldehyde gives >98:2 *anti*:*syn* and 98:2 selectivity *anti*:*anti*) and the *Z*-enolate (Bu_2BOTf, $^iPr_2NEt$, -78 °C, 2 h, then isobutyraldehyde gives 87:13 *syn*:*anti* and 96:4 selectivity *syn*:*syn*), it is only possible to access the *E*-enolate with reasonable selectivity for the thiol analogue. This suggests that there could be a significant difference in the ground state energies of the *Z*- and *E*-enolates for the thiol derivative and not for the Abiko-Masamune auxiliary, and therefore that the *Z*-enolate of the thiol analogue would not be accessible.

Previous reports of boron enolisation for thiolesters have shown that bulky thiolesters, such as $^{t}BuSC(O)CH_2CH_3$, typically produce *E*-enolates under the enolisation conditions, to give *anti*-aldol adducts in high *anti*:*syn* diastereoselectivity (**table 7**, entries 1-6)[73,101-106]. The oxygenated counterpart has also been successfully enolised by Corey[107] (**table 7**, entry 7) and Abiko[33] (**table 7**, entry 8).

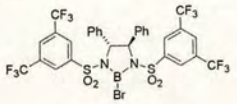


Entry	X	Enolisation Conditions	Solvent	ds (*anti* : *syn*)	Ref.
1	S	$(^{c}Pen)_2BOTf$ / $^{i}Pr_2NEt$	Et_2O	> 95:5	101
2	S	Bu_2BOTf / $^{i}Pr_2NEt$	Et_2O	> 95:5[a]	102
3	S	$(^{c}Hex)_2BOTf$ / Et_3N	Et_2O or pentane	> 97:3	103
4	S	R_2BBr[b] / Et_3N	Et_2O or CH_2Cl_2	> 98:2[a]	104,105
5	S	$(^{c}Hex)_2BCl$ / Et_3N	CH_2Cl_2	> 95:5	106
6	S	$(^{c}Hex)_2BBr$ / Et_3N	Et_2O	> 95:5	73
7	O	R_2BBr[c] / Et_3N	CH_2Cl_2	> 94:6	107
8	O	$(^{c}Hex)_2BOTf$ / Et_3N	CH_2Cl_2	> 97:3	33

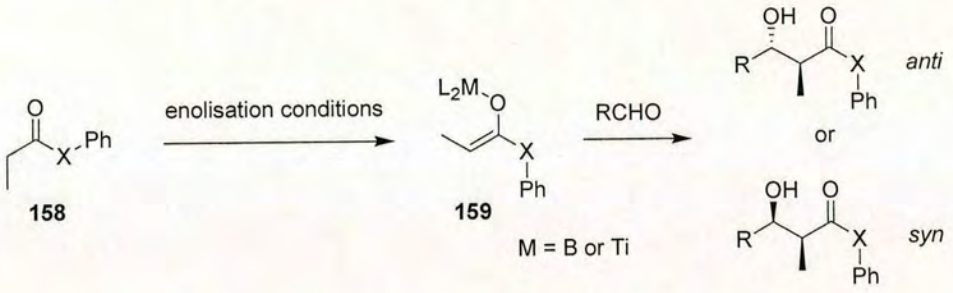
Table 7: *Anti*-selective enolisation of bulky thiolesters. [a] *E*:*Z* enolisation. [b] R_2BBr =



[c] R_2BBr =

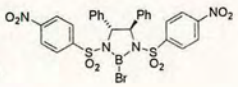


However, smaller thiolesters, such us $PhSC(O)CH_2CH_3$, allow *Z*-selective enolisation to generate *syn*-aldol products (**table 8**, entries 1-4).[108-111] Although there are no boron enolisation examples previously reported in the literature for the oxygenated counterpart, *Z*-selective enolisation with titanium (**table 8**, entry 5) gives *syn*-aldol adducts with good diastereoselectivities (*syn*:*anti* > 89:11).[112,113]



Entry	X	Enolisation Conditions	Solvent	ds (*syn* : *anti*)	Ref.
1	S	9-BBN-OTf / $^iPr_2NEt$	Et_2O	> 95:5	108
2	S	9-BBN-OTf / $^iPr_2NEt$	Et_2O	> 95:5	109
3	S	R_2BBr^a / $^iPr_2NEt$	CH_2Cl_2	> 96:4	110
4	S	9-BBN-OTf / $^iPr_2NEt$	Et_2O	> 95:5	111
5	O	$TiCl_4$ / Et_3N	CH_2Cl_2	> 89:11	112,113

Table 8: *Syn*-selective enolisation of less hindered thiolesters. [a] R_2BBr =

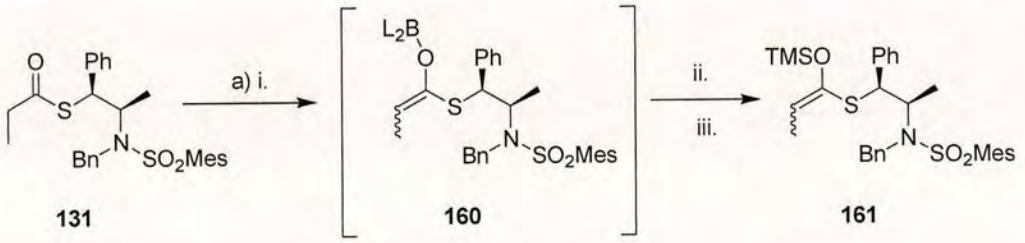


Thus, considering our sulfur analogue of the Abiko-Masamune auxiliary as a bulky thiolester, the literature precedent for *E*-selective enolisation of bulky thiolesters, could explain the absence of *syn* aldol adducts observed in our experimental results.

2.4.2 Enolisation Studies

In order to prove the geometry of the enolate, enolisation studies were carried out under both the *anti* and syn-selective conditions reported by Abiko.[33]

A method reported to be effective for the assignment of *Z*- and *E*-enolate geometry of silyl enol ethers was initially investigated.[102,114-116] Thiolester **131** was treated with triflate and base at -78 °C to generate boron enolates **160**. Transmetalation with butyl-lithium followed by derivatisation with trimethylsilyl chloride was carried out in an attempt to isolate trimethylsilyl enol ethers **161** (**scheme 48**). It has been reported that the vinyl proton in an *E*-diastereoisomer generally resonates downfield of the corresponding proton in the *Z*-diastereoisomer.[115,116] However, this method is not always possible due to the narrow difference in the resonances of the stereoisomeric pair (0.06-0.07 ppm). Although analysis by proton NMR is not always possible, assignment of enolate geometry by carbon NMR is straightforward and unambiguous. It is well established that the vinyl carbons in *cis*-alkenes resonate at higher field than those in *trans*-alkenes. The shift is typically 5-6 ppm. The same effect can be observed in stereoisomeric silyl enol ethers.[117-119] Thus, isolation and subsequent NMR analysis of silyl enol ethers **161** was performed in an attempt to prove the geometry of the boron enolate.



131 **160** **161**

Scheme 48: Study of enolate geometry by silyl enol ether formation. Reagents and conditions: a) i. c-Hex_2BOTf/Et_3N or $Bu_2BOTf/^iPr_2NEt$, CH_2Cl_2, 2 h, -78 °C; ii. BuLi, 5 h, -78 °C; iii. TMSCl, 14 h, RT.

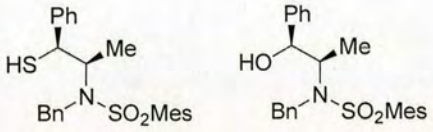
Although different attempts to isolate silyl enol ethers **161** were undertaken, including the use of TBDMSCl to generate more stable silyl enol ethers, only thiolester **131** was observed by NMR analysis in all cases.

When an aliquot of a solution of thiolester **131**, Bu_2BOTf and $^iPr_2NEt$ in deuteriated chloroform at -78 °C was taken for NMR analysis, again only thiolester **131** was observed, suggesting the high instability of the boron enolate.

2.5 CONCLUSION

2.5.1 Improvement of the Route towards the Synthesis of Sulfur Auxiliary 117

An improved route to a thiol derivative **117** of the Abiko-Masamune auxiliary **162** was developed (from six steps and > 44% overall yield, to five steps and > 71%; **scheme 37**).[92]

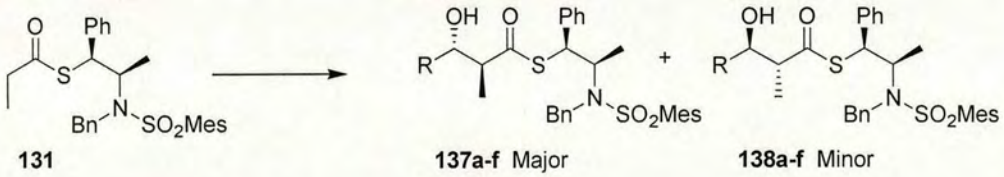


117 **162**

Figure 18: New thiol chiral auxiliary **117** and Abiko-Masamune auxiliary **162**.

2.5.2 *Anti*-Propionate Aldols and Proof of Relative and Absolute Stereochemistry

Anti propionate aldol adducts **137a-f** and **138a-f** were synthesised in excellent *anti*:*syn* diastereoselectivity (> 98:2) and *anti*:*anti* diastereofacial selectivity (> 91:9; **table 2**).[91,92]



131 **137a-f** Major **138a-f** Minor

Scheme 49: Synthesis of *anti* propionate aldols using sulfur auxiliary **117**.[91,92]

The relative stereochemistry of *anti* aldols **137a-f** and **138a-f** was assigned by NMR analysis of coupling constants between vicinal protons. The absolute stereochemistry was proved by optical rotation values of acid and diol derivatives and their agreement with the literature.

2.5.3 *Syn*-Propionate Aldols

A number of attempts were pursued in order to synthesise *syn*-propionate aldol adducts, including the investigation of changes in enolisation reagents and reaction conditions. Unfortunately, all the conditions studied failed to produce significant amounts of *syn* aldol adducts and only an erosion of the *anti*:*anti* facial selectivity was observed in all cases.

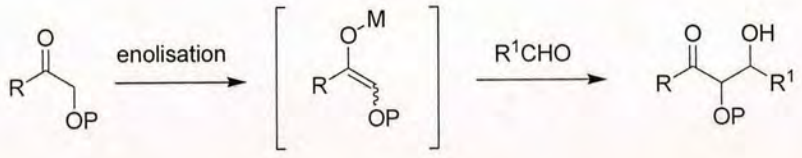
2.5.4 Rationalisation Studies

Based on our experimental results, in which only *anti* propionate aldol adducts were obtained to a high extension under a range of different enolisation conditions, it appears that while both the *E*-enolate and the *Z*-enolate are accessible with the Masamune auxiliary, only *E*-enolisation can be achieved with the sulfur auxiliary. Considering our sulfur auxiliary as a bulky thiolester, our experimental results would be in good agreement with previous reports of boron enolisation for thiolesters in the literature, in which *E*-selective enolisation is achieved with bulky thiolesters such as $^{t}BuSC(O)CH_2CH_3$,[73,101-106] while *Z*-selective enolisation is accessible with less hindered thiolesters such as $PhSC(O)CH_2CH_3$.[108-111] However, we were unable to show this directly from *E*-selective enolisation studies.

CHAPTER 3: RESULTS AND DISCUSSION 2

3.1 GLYCOLATE ALDOL REACTION IN SYNTHESIS

Glycolate aldol reactions have been extensively used in synthesis to produce 1,2-diol products as an alternative method to double bond dihydroxylation.



Scheme 50: Use of glycolate aldols to afford 1,2-diols.

Various auxiliary-based approaches have been reported to successfully obtain the desired products. In the majority of cases a boron enolate of the Evans oxazolidinone glycolate is used to generate the *syn* aldol adducts.[26-29,120-123] In addition, the titanium enolates of Evans' oxazolidinones and oxazolidinethiones have also demonstrated to give high *syn* selectivities.[124,125] Other successful auxiliary-based strategies include the use of Abiko-Masamune norephedrine esters, which have been effectively used in the synthesis of *syn* glycolate aldols by Andrus.[65,66]

Effective methods to obtain *anti*-aldol adducts from glycolate enolates are less prevalent. Moderately selective *anti*-aldol reactions of tin(II) enolates of oxazolidinones and thiazolidinethiones have been observed by Mukayama-Kobayashi[126-128] and Evans.[129] However, Crimmins[130,131] has reported a highly *anti*-selective aldol reaction with titanium enolates of oxazolidinethiones. The reaction proceeds via an open transition state similar to the one described for their propionate counterparts by Heathcock (**scheme 23**),[68-70] due to aldehyde activation by an excess of Lewis acid. Alternative auxiliary-based approaches include the use of oxapyrone boron-enolates[132,133] or titanium enolates of oxazolidin-2-selones.[134]

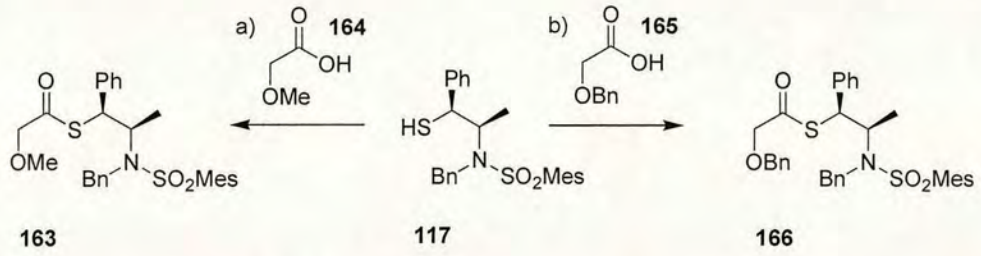
Catalytic approaches to glycolate aldol reactions have also been investigated in recent years;[135,136] Kobayashi's tin glycolates, with good selectivity for either the *syn* or *anti* diols, remain among the prime examples.[137,138]

3.2 SYNTHESIS OF *SYN* GLYCOLATE ALDOLS

3.2.1 Use of the Optimised Conditions for the Abiko-Masamune Auxiliary

Andrus has reported the use of Abiko-Masamune norephedrine glycolate esters to produce *syn*-aldol adducts with a range of aldehydes in high yields (>75%) and variable diastereoselectivities (*syn*:*syn* from 67:33 to 97:3).[65] Interestingly, the optimised conditions found by Andrus to give *syn* glycolate aldols were coincident with those reported by Abiko to afford *anti* propionate products (c-Hex_2BOTf/Et_3N).[33,65]

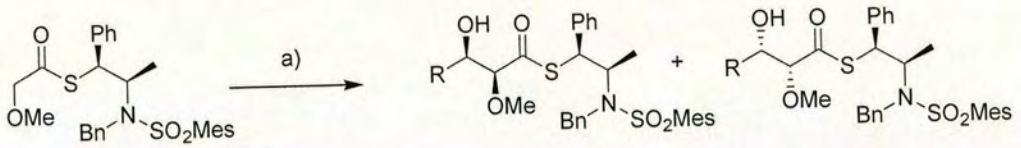
In our initial investigations we decided to test the optimised conditions developed by Andrus with our sulfur analogue of the Abiko-Masamune auxiliary. Preparation of glycolate thiolesters **163** and **166** was performed following an analogous procedure to the one described by Andrus.[65] Coupling of thiol auxiliary **117** with methoxyacetic acid **164** using catalytic DMAP and the coupling reagent EDCI in CH_2Cl_2 afforded glycolate thiolester **163** in good yield. A slight variation on the conditions reported by Andrus (use of coupling reagent DIC instead of EDCI), also gave **166** in comparable yield (**scheme 51**).



163 **117** **166**

Scheme 51: Synthesis of glycolate thiolesters. Reagents and conditions: a) methoxyacetic acid **164** (1.1 eq.), DMAP (10 mol%), EDCI (1.1 eq.), CH_2Cl_2, 2 h at 0 °C then 14 h at RT (71%). b) benzyloxyacetic acid **165** (1.2 eq.), DMAP (10 mol%), DIC (1.2 eq.), CH_2Cl_2, 2 h at 0 °C then 14 h at RT (69%).

Treatment of glycolate thiolester **163** under Andrus' optimised conditions afforded *syn* glycolate aldol adducts with a range of aldehydes in good yields and excellent *syn*:*anti* diastereoselectivities (>98:2). In contrast, we found lower *syn*:*syn* selectivities (around 65:35) showing an erosion in the facial selectivity compared to its oxygenated counterpart (**table 9**).



163 **167c-e** Major **168c-e** Minor

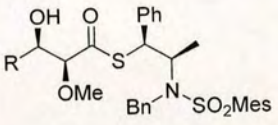
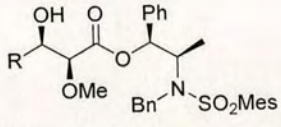
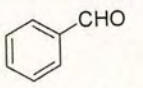
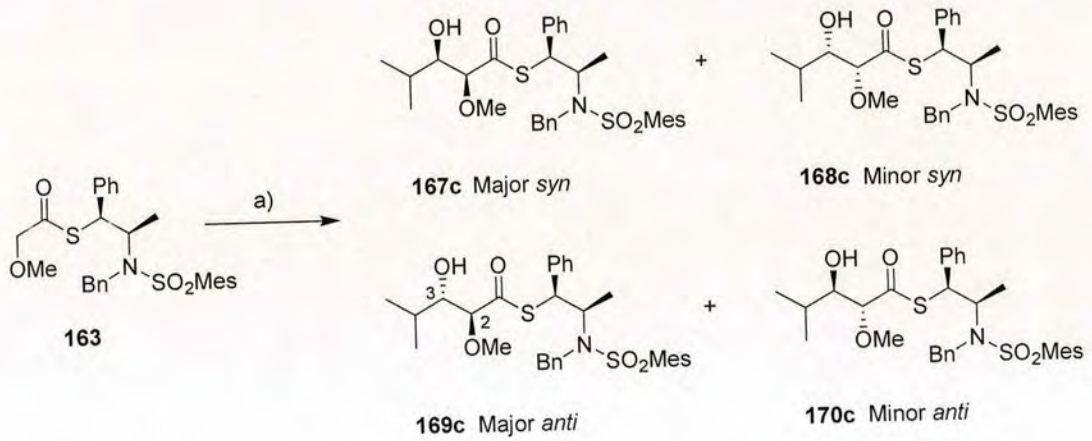
			
Aldehyde		Yield (%) / ds (*syn* : *syn*)[b]	Yield (%) / ds (*syn* : *syn*)
c		67 (65 : 35)	88 (96 : 4)[65]
d		90 (66 : 34)	92 (93 : 7)[65]
e		95 (66 : 34)	87 (97 : 3)[65]

Table 9: Synthesis of *syn*-glycolate aldols under the optimised conditions for Abiko-Masamune norephedrine glycolate esters.[65] Reagents and conditions: a) c-Hex_2BOTf (3.0 eq.), Et_3N (2.5 eq.), CH_2Cl_2, -78 °C for 2 h; then aldehyde (3.0 eq.), -78 °C for 2 h, 0 °C for 1 h. [b] by NMR and HPLC of diastereomeric mixture.

3.2.2 Assignment of Relative Stereochemistry

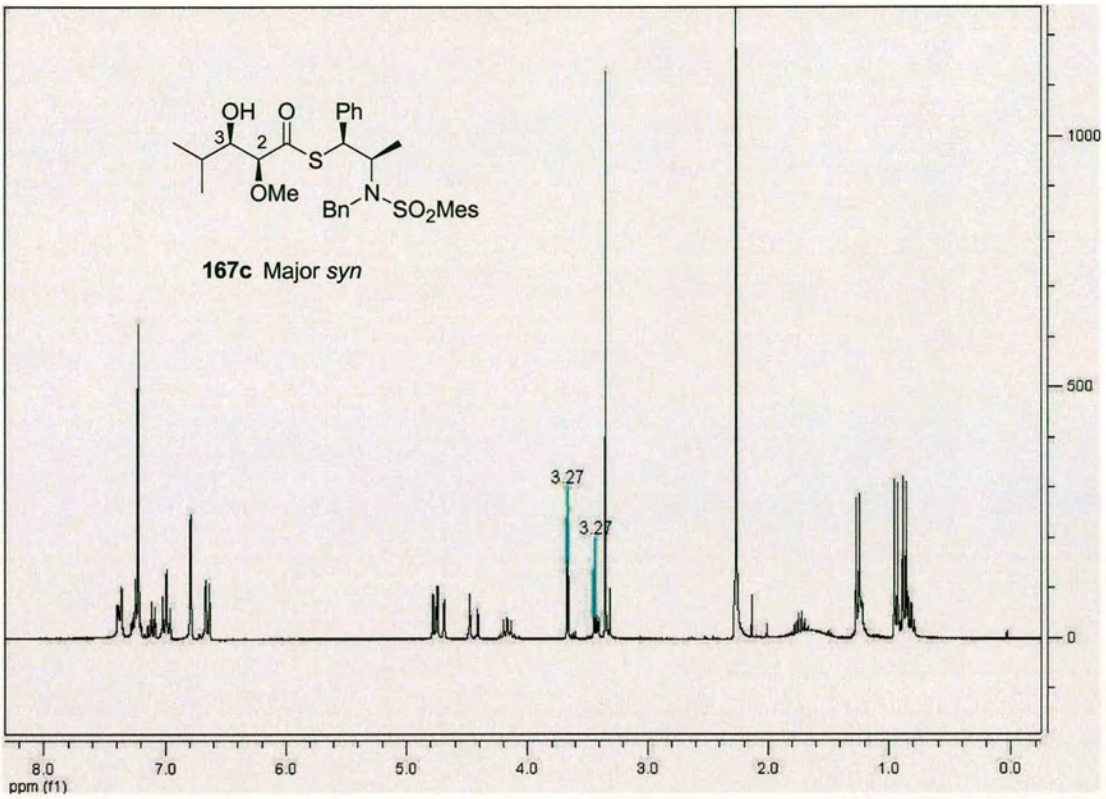
As described before for the propionate aldols (**figure 12**), the relative stereochemistry of the four possible diastereoisomers was assigned on the basis of the coupling constant value between C2 and C3 protons in the aldol adducts generated.

For example, NMR analysis of the four glycolate diastereoisomers generated from isobutyraldehyde (**scheme 52**) allowed assignment of *syn* and *anti* stereochemistry of the aldol adducts.



Scheme 52: Four possible glycolate diastereoisomers from isobutyraldehyde. Reagents and conditions: a) $cHex_2BOTf$ (3.0 eq.), Et_3N (2.5 eq.), CH_2Cl_2, -78 °C for 1 h; then isobutyraldehyde (3.0 eq.), -78 °C for 4 h, 0 °C for 1 h (67 %, *syn*:*syn* = 65:35, *syn*:*anti* = 98:2; by NMR and HPLC of diastereomeric mixture).

Analysis of NMR coupling constants between the C2 and C3 protons, allowed assignment of the *syn* stereochemistry of aldol adduct **167c** (3.3 Hz in **figure 19**) and **168c** (4.0 Hz in **figure 20**). In both NMR spectra a small amount of *anti* diastereoisomer was also detected (minor *anti* aldol **170c** with coupling constant 6.1 Hz and major *anti* product **169c** with coupling constant 6.6 Hz respectively). NMR of major *anti* aldol adduct **169c** (**figure 21**) showed a coupling constant value of 6.6 Hz and the same for minor *anti* aldol product **170c** (**figure 22**) gave a 6.1 Hz coupling constant (here, a small amount of major *syn* aldol **167c** was also detected).



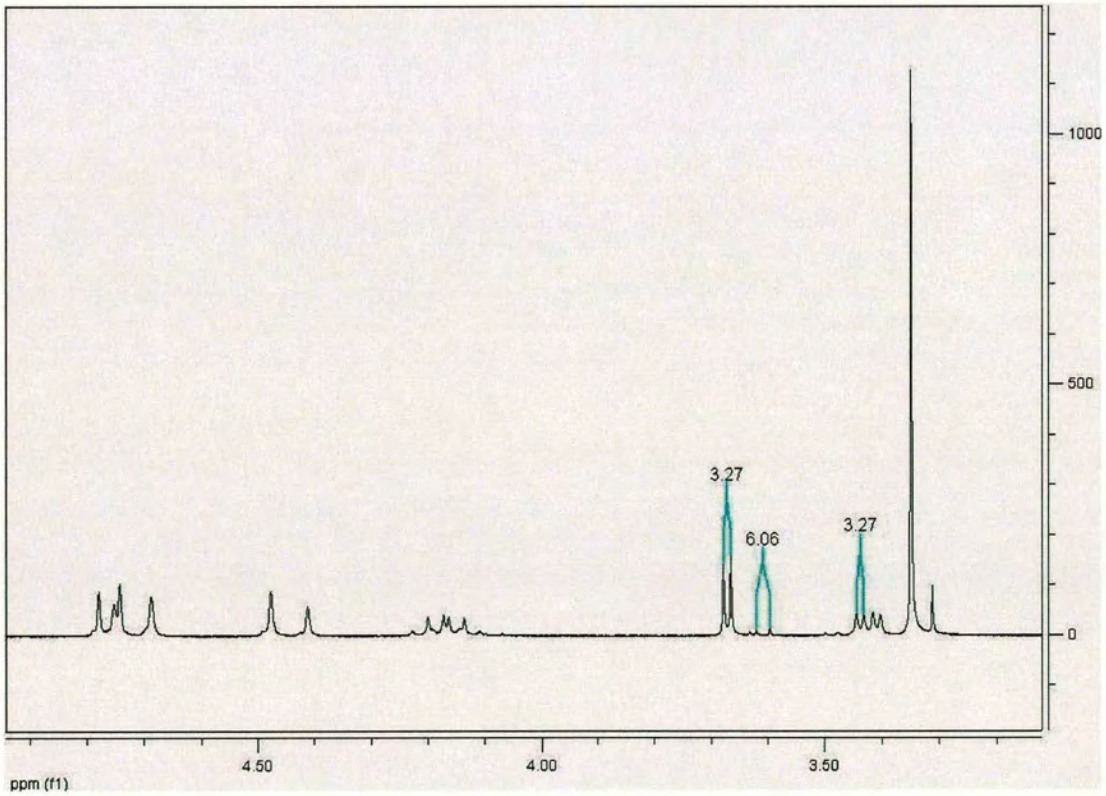
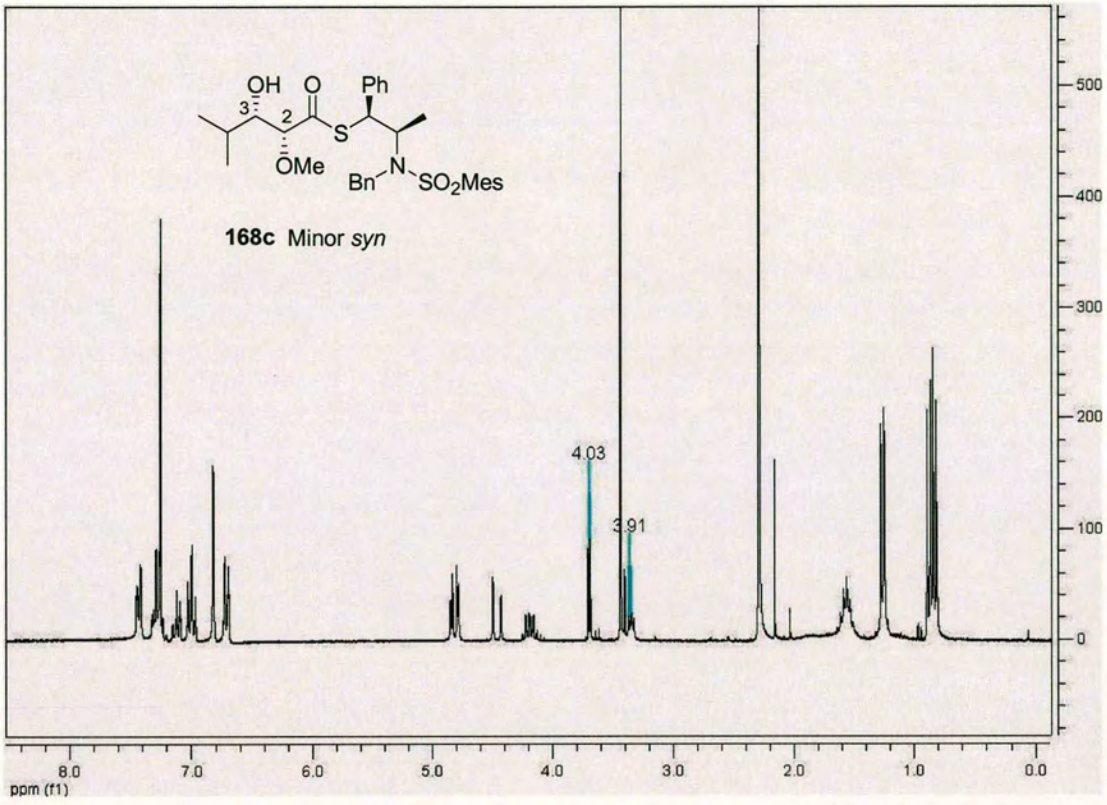


Figure 19: The NMR of major *syn*-aldol adduct **167c** and its expansion, showing the coupling constant between C2 and C3 protons.



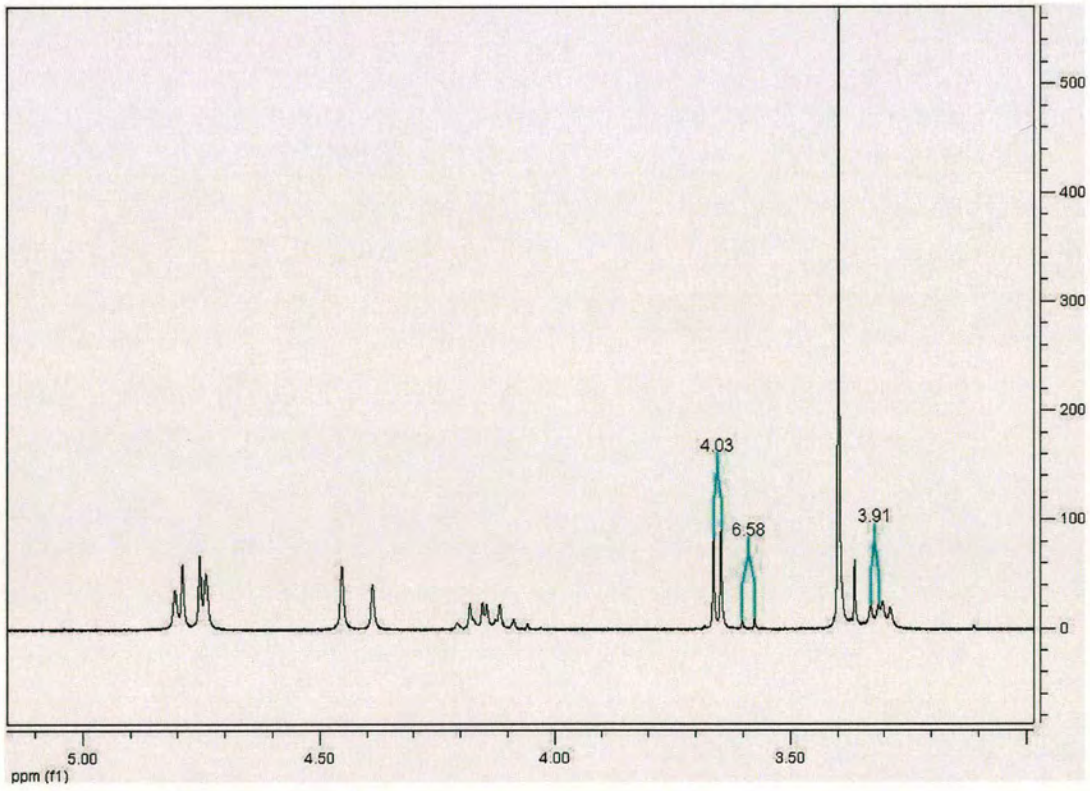
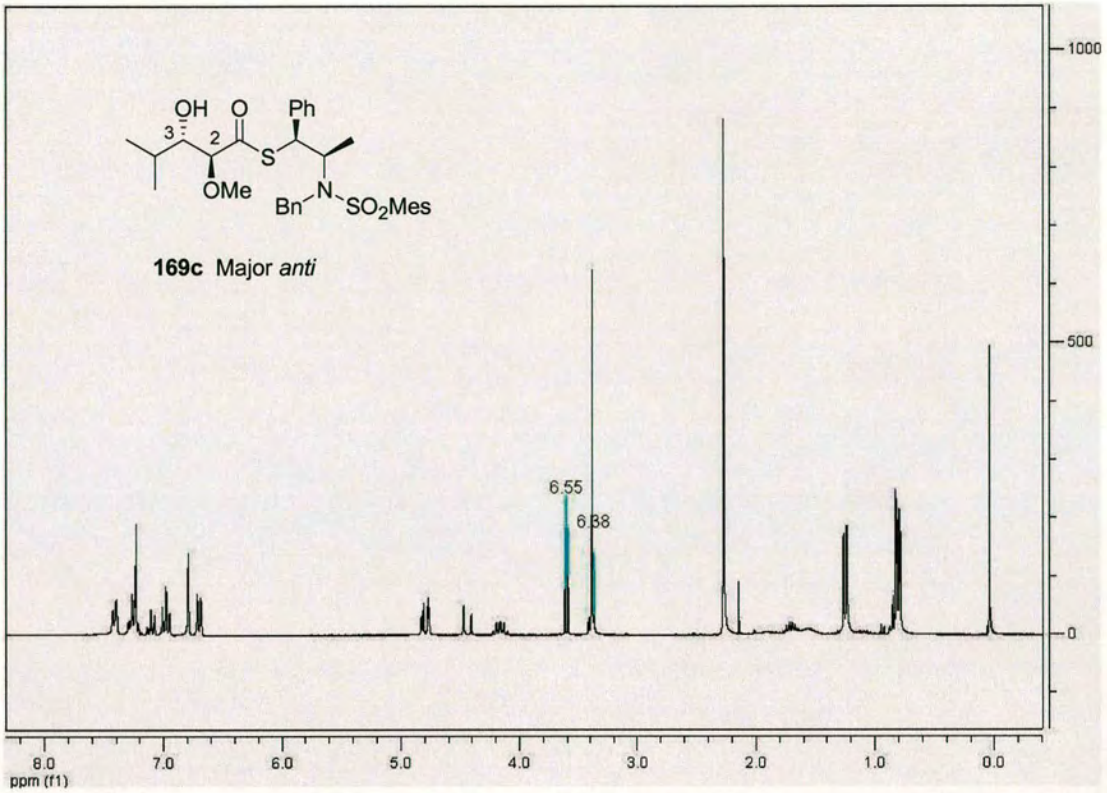


Figure 20: The NMR of minor *syn*-aldol adduct **168c** and its expansion, showing the coupling constant between C2 and C3 protons.



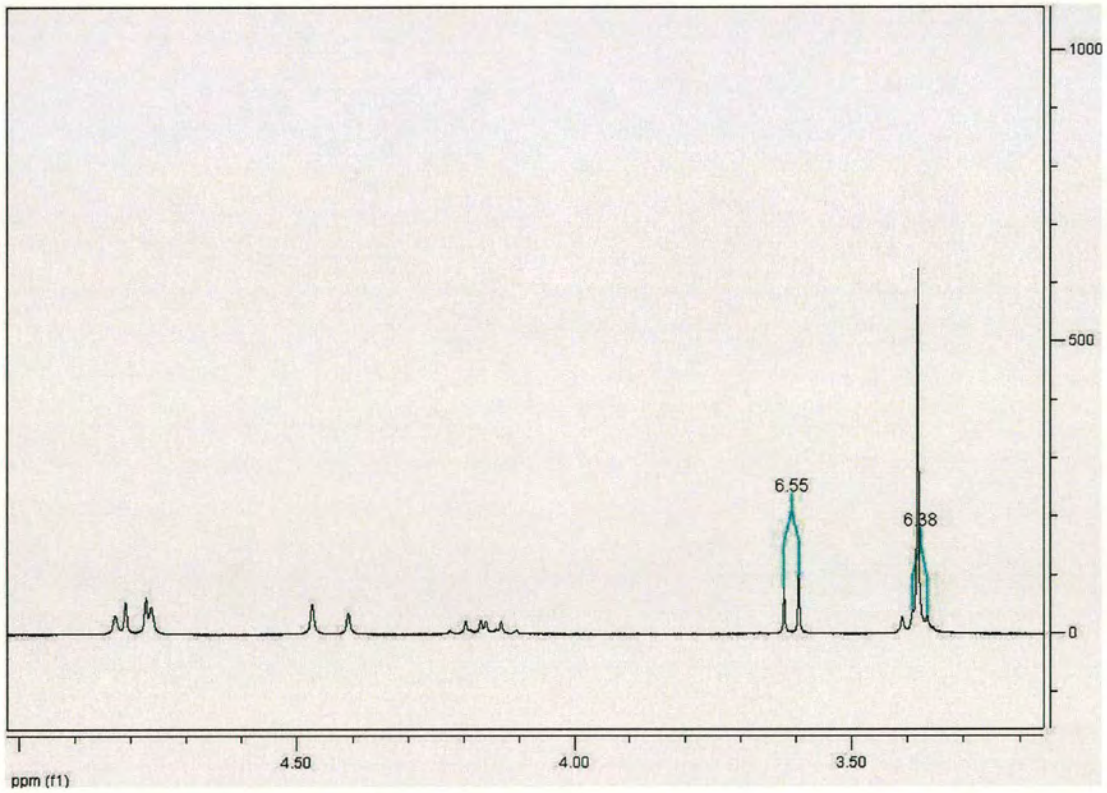
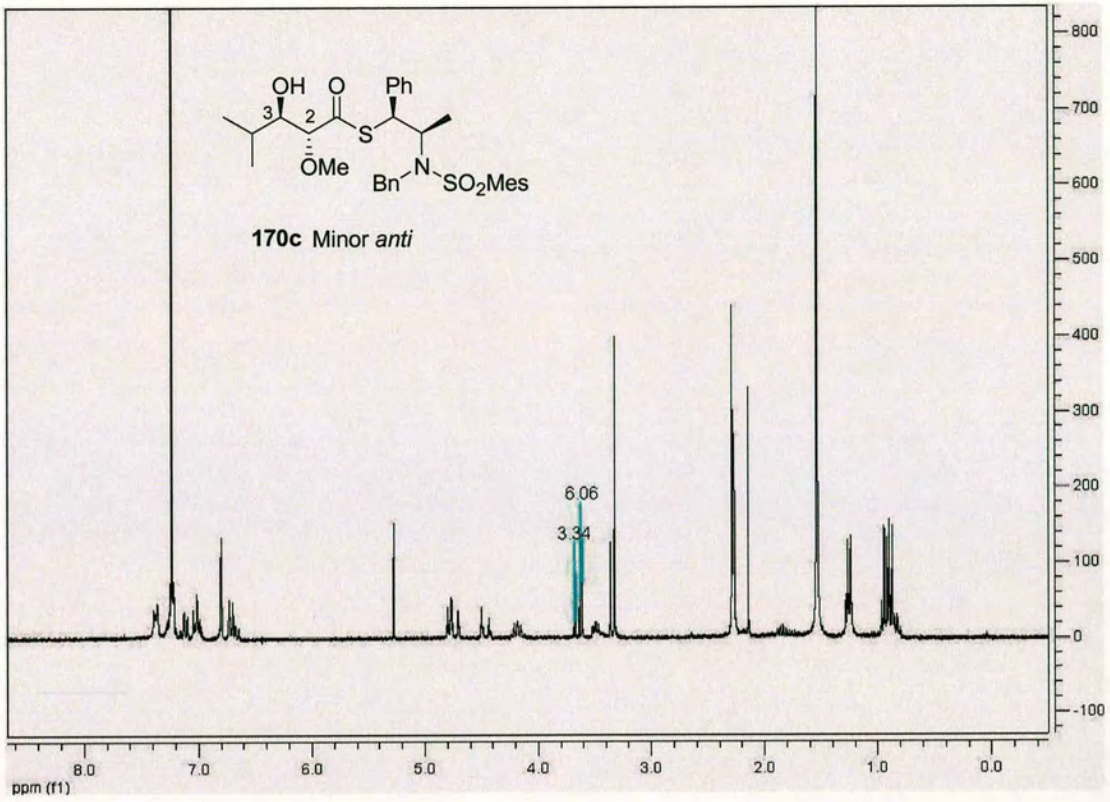


Figure 21: The NMR of major *anti*-aldol adduct **169c** and its expansion, showing the coupling constant between C2 and C3 protons.



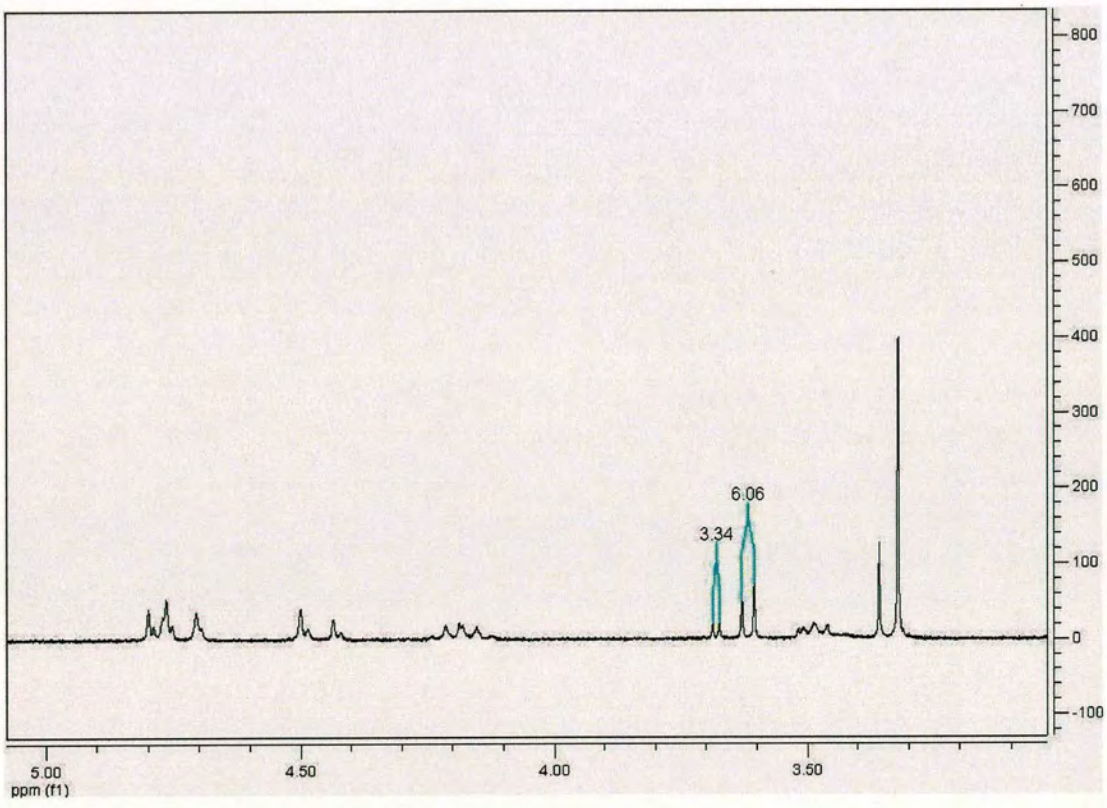


Figure 22: The NMR of minor *anti*-aldol adduct **170c** and its expansion, showing the coupling constant between C2 and C3 protons.

3.2.3 Proof of Absolute Stereochemistry

The absolute stereochemistry of major *syn*-glycolate aldol **167e** was proved by X-ray crystal structure, demonstrating agreement with the stereochemistry previously reported with the Abiko-Masamune auxiliary.[65]

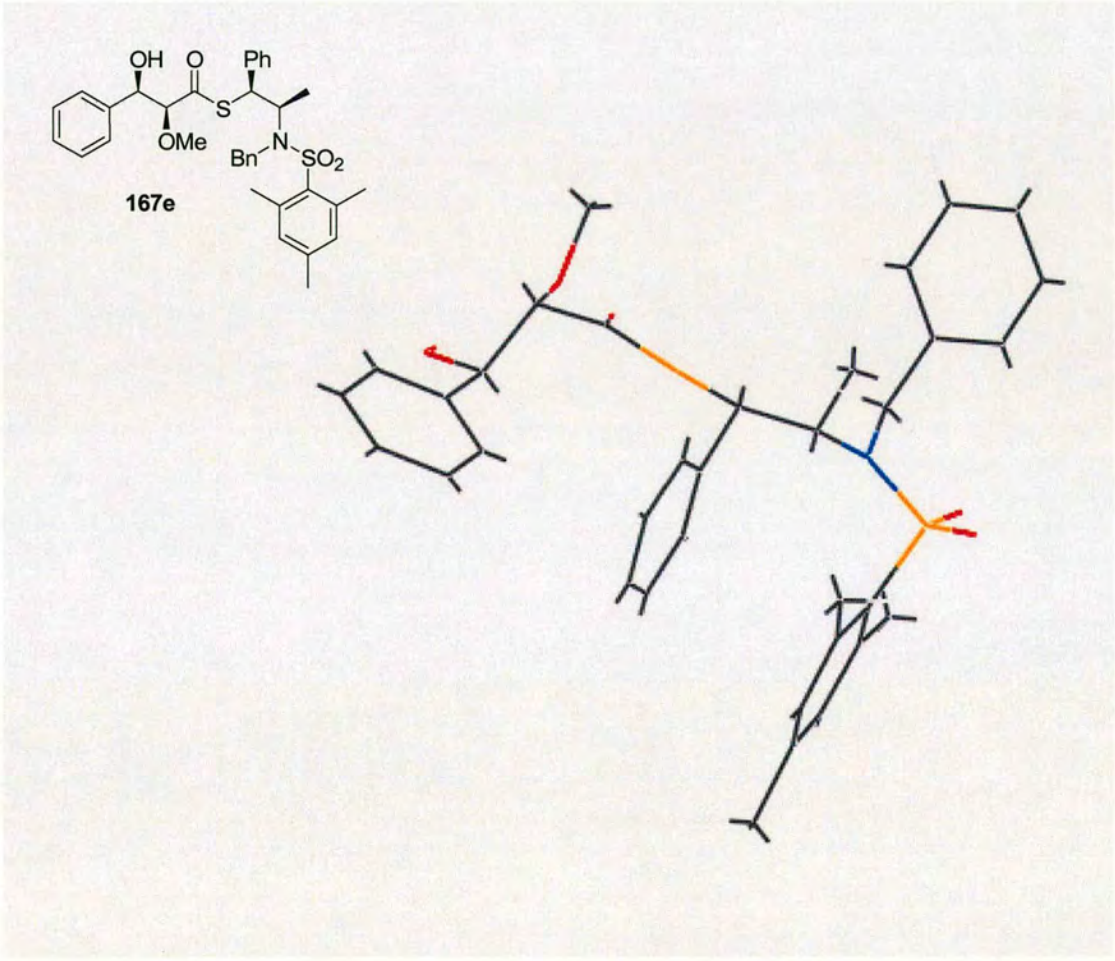


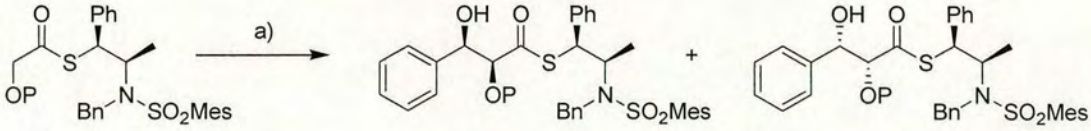
Figure 23: X-ray crystal structure of major *syn*-adol adduct **167e**.

The absolute stereochemistry of the minor *syn*-glycolate aldol adducts **168a-c** was assigned as the other possible *syn*-diastereoisomer.

3.2.4 Investigation of the effects of Different Bases and Triflates on Enolisation

Disappointed with the level of facial selectivity achieved using the optimised conditions reported for the Abiko-Masamune auxiliary, we decided to investigate the use of different protecting groups (Me- and Bn-groups) and various combinations of triflates and bases, to study their potential influence on the stereochemical outcome of the reaction. All these reactions were carried out with benzaldehyde as it was the aldehyde reported to give the best selectivities by Andrus.[65] Under all the conditions investigated excellent *syn*:*anti* diastereoselectivities were obtained (>91:9). Interestingly, although there was not significant improvement in the *syn*:*syn* diastereofacial selectivity, inversion of facial selectivity was observed depending on the ligand involved. While the major aldol adducts produced with c-Hex_2BOTf were those with the same stereochemistry of the glycolate ester precedent *syn* 1 (**table 10**, entries 1 and 2),[65] Bu_2BOTf and 9-BBNOTf afforded the other *syn*-aldol adduct *syn* 2 as the major diastereoisomer (**table 10**, entries 3-6).

Andrus[65] also investigated the influence that different ligands could have on the stereochemistry of the aldol products, but no switch in the facial selectivity was reported with the Abiko-Masamune auxiliary. The use of c-Hex_2BOTf with either Et_3N or $^iPr_2NEt$ afforded *syn*-aldol adducts with isobutyraldehyde in high *syn*:*syn* selectivity (96:4 *syn*1:*syn*2 for the Me-protected ester, entries 1 and 2, **table 11**; 95:5 *syn*1:*syn*2 with the Bn-protected substrate, entries 1 and 2, **table 11**). In contrast, $Bu_2BOTf/^iPr_2NEt$ gave a lower yield and diastereoselectivity (30%, 75:25 *syn*1:*syn*2, entry 4, **table 11**), while only traces of products were recovered with Bu_2BOTf/Et_3N (entry 3, **table 11**) (both with Bn-protected glycolate ester, isobutyraldehyde).



syn 1

P = Me, **167e**

P = Bn, **171e**

syn 2

P = Me, **168e**

P = Bn, **172e**

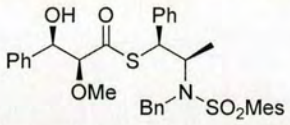
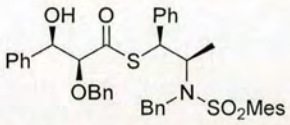
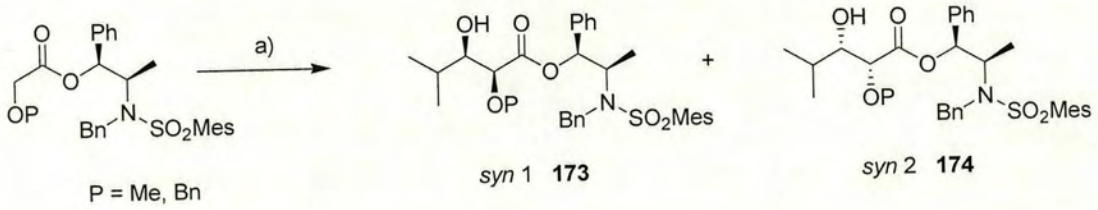
			
ıtry	Triflate / Base	Yield (%) / ds (*syn*1 : *syn*2) // ds (*syn* : *anti*)[b]	Yield (%) / ds (*syn*1 : *syn*2) // ds (*syn* : *anti*)[b]
1	(^{c}Hex)$_2$BOTf / Et_3N	90 (66 : 34) // (91 : 9)	90 (74 : 26) // (99 : 1)
2	(^{c}Hex)$_2$BOTf / ^{i}Pr$_2$NEt	85 (68 : 32) // (95 : 5)	84 (65 : 35) // (99 : 1)
3	9-BBN-OTf / Et_3N	73 (21 : 79) // (99 : 1)	80 (31 : 69) // (93 : 7)
4	9-BBN-OTf / ^{i}Pr$_2$NEt	80 (47 : 53) // (96 : 4)	79 (43 : 57) // (97 : 3)
5	Bu_2BOTf / Et_3N	84 (26 : 74) // (91 : 9)	82 (36 : 64) // (99 : 1)
6	Bu_2BOTf / ^{i}Pr$_2$NEt	78 (31 : 69) // (98 : 2)	74 (28 : 72) // (94 : 6)

Table 10: Synthesis of *syn*-glycolate aldols with different bases and triflates. Reagents and conditions: a) Boron Triflate (3.0 eq.), Base (2.5 eq.), CH_2Cl_2, -78 °C for 1 h; then benzaldehyde (3.0 eq.), -78 °C for 2 h, 0 °C for 1.5 h. [b] by NMR and HPLC of diastereomeric mixture



syn 1 **173**

syn 2 **174**

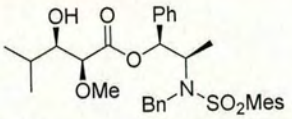
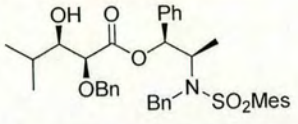
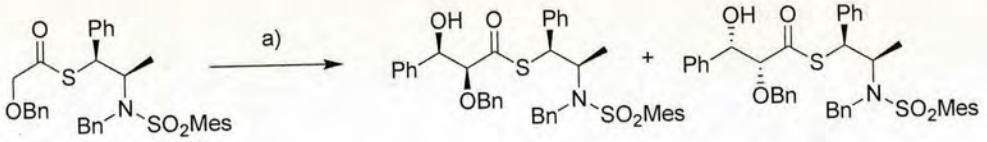
			
Entry	Triflate / Base	Yield (%) / ds (*syn*1 : *syn*2)	Yield (%) / ds (*syn*1 : *syn*2)
1	$(^{c}Hex)_2BOTf$ / Et_3N	88 (96 : 4)[65]	98 (95 : 5)[65]
2	$(^{c}Hex)_2BOTf$ / $^{i}Pr_2NEt$	88 (96 : 4)[65]	88 (95 : 5)[65]
3	Bu_2BOTf / Et_3N	------	3 (Not determined)[65]
4	Bu_2BOTf / $^{i}Pr_2NEt$	------	30 (75 : 25)[65]

Table 11: Synthesis of Masamune *syn*-glycolate aldols with different bases and triflates.[65] Reagents and conditions: a) Boron Triflate (3.0 eq.), Base (2.5 eq.), CH_2Cl_2, -78 °C; then isobutyraldehyde (1.2 eq.), from -78 °C to 0 °C.

3.2.5 Investigation of the Effects of Enolisation Temperature

We also studied the influence that the temperature could have on the enolisation process. When the reaction was carried out at 0 °C under $Bu_2BOTf/^iPr_2NEt$ no significant change in the *syn*:*anti* selectivity was detected (94:6 at -78 °C and 93:7 at 0 °C). In contrast, some erosion in the *syn*:*syn* facial selectivity was observed (28:72 at -78 °C and 42:58 at 0 °C). When $cHex_2BOTf/Et_3N$ was used at 0 °C a significant increase in the amount of *anti*-aldol products was detected (*syn*:*anti* 99:1 at -78 °C and 68:32 at 0 °C), suggesting possible isomerisation between the *Z*- and *E*-enolate at higher temperatures (although these were results obtained after a single attempt). In order to prove this, the enolisation was carried out at room temperature. Surprisingly, the results obtained in this case were similar to those detected at -78 °C (*syn*:*anti* 99:1 at -78 °C, 68:32 at 0 °C and 93:7 at RT). Erosion in the facial selectivity was also observed at higher temperatures (*syn*:*syn* 74:26 at -78 °C, 55:45 at 0 °C and 62:38 at RT) (**table 12**).



166 *syn* 1 **171e** *syn* 2 **172e**

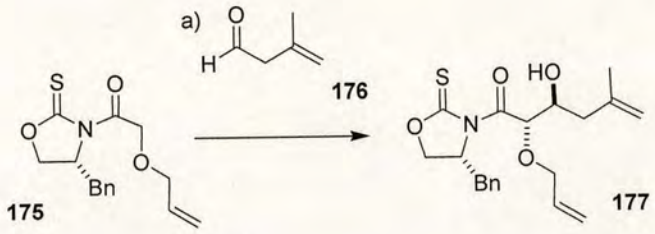
	$(^cHex)_2BOTf$ / Et_3N	Bu_2BOTf / $^iPr_2EtN$
Temperature	Yield (%) / ds (*syn*1 : *syn*2) // ds (*syn* : *anti*)[b]	Yield (%) / ds (*syn*1 : *syn*2) // ds (*syn* : *anti*)[b]
-78 °C	90 (74 : 26) // (99 : 1)	74 (28 : 72) // (94 : 6)
0 °C	60 (55 : 45) // (68 : 32)	68 (42 : 58) // (93 : 7)
RT	88 (62 : 38) // (93 : 7)	----------

Table 12: *Syn* glycolate aldol enolisations carried out at different temperatures. Reagents and conditions: a) Boron Triflate/Base in CH_2Cl_2, at -78 °C, 0 °C or room temperature for 1 h; then PhCHO at the same temperature. [b] by NMR and HPLC of diastereomeric mixture.

3.3 SYNTHESIS OF *ANTI* GLYCOLATE ALDOLS

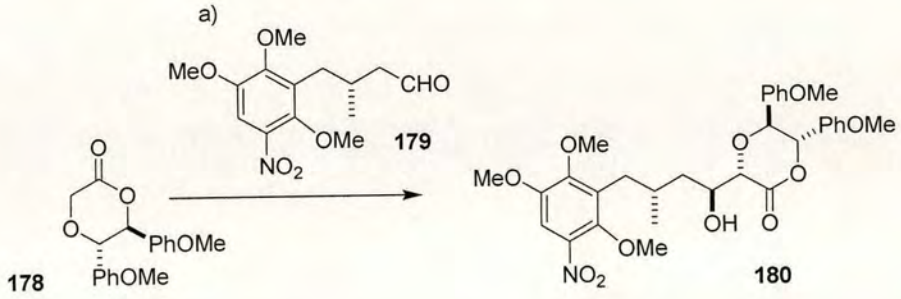
3.3.1 Auxiliary-Controlled *Anti* Glycolate Aldol Reactions in Synthesis

Very few examples of auxiliary-based *anti*-glycolate aldols have been previously reported in the literature. The selective *anti*-aldol reaction of titanium enolates of oxazolidinethiones developed by Crimmins[130] has been successfully used in the stereoselective synthesis of the BCDE fragment of Brevetoxin A,[131] where a good yield (64%) and selectivity (87:2:11, *anti*:*anti*:*syn*) were achieved (**scheme 53**).



Scheme 53: Use of Crimmins' *anti*-glycolate methodology in the synthesis of the BCDE fragment of Brevetoxin A.[131] Reagents and conditions: a) $TiCl_4$, (-)-sparteine, CH_2Cl_2, -78 °C, 1 h, then **176** and $TiCl_4$, 15 min (64%, 87:2:11, *anti*:*anti*:*syn*).

The *anti*-selective boron-mediated glycolate aldol reaction using a diaryldioxanone auxiliary **178** developed by Andrus[132] has been used in the synthesis of (+)-geldanamycin, affording a good yield (70%) and excellent diastereoselectivity (>91:9) (**scheme 54**).[66,133]

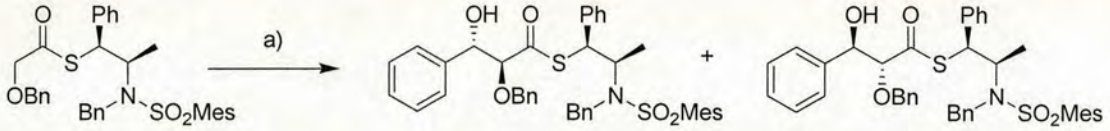


Scheme 54: Use of Andrus' *anti*-glycolate methodology in the synthesis of (+)-geldanamycin.[66,133] Reagents and conditions: a) c-Hex_2BOTf, Et_3N, CH_2Cl_2, -78 °C, 2 h, then **179**, -78 °C, 2 h (70%, ds >91:9).

3.3.2 Synthesis of *Anti* Glycolate aldols

As described before, Andrus[65] has reported the use of Abiko-Masamune norephedrine glycolate esters to produce *syn*-aldol adducts with a range of aldehydes in high yields and diastereoselectivities. However, there are no examples in the literature of *anti*-selective glycolate aldol reactions involving the Abiko-Masamune auxiliary.

When thiolester **166** was treated with dicyclohexylboron chloride and a base, *anti*-aldol adducts were produced in very high *anti*:*syn* diastereoselectivities (>94:6), suggesting *E*-enolate formation, in contrast to the ester precedent. Use of these well-known conditions for *E*-enolisation (and also $TiCl_4$ and tin (II) triflate) were reported to be ineffective with the ester analogue by Andrus.[65] However, use of dicyclohexylboron chloride with different bases and solvents proved to be highly effective in the synthesis of *anti*-aldol adducts in excellent *anti*:*syn* diastereoselectivities, with the sulfur analogue of the Abiko-Masamune auxiliary (**table 13**).



166 Major **181e** Minor **182e**

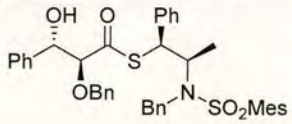
	
Base / Solvent	Yield (%) / ds (*anti* : *anti*) // ds (*anti* : *syn*)[b]
Et_3N / CH_2Cl_2	98 (77 : 23) // (98 : 2)
$^iPr_2NEt$ / CH_2Cl_2	49 (71 : 29) // (94 : 6)
Et_3N / Ether	92 (77 : 23) // (99 : 1)

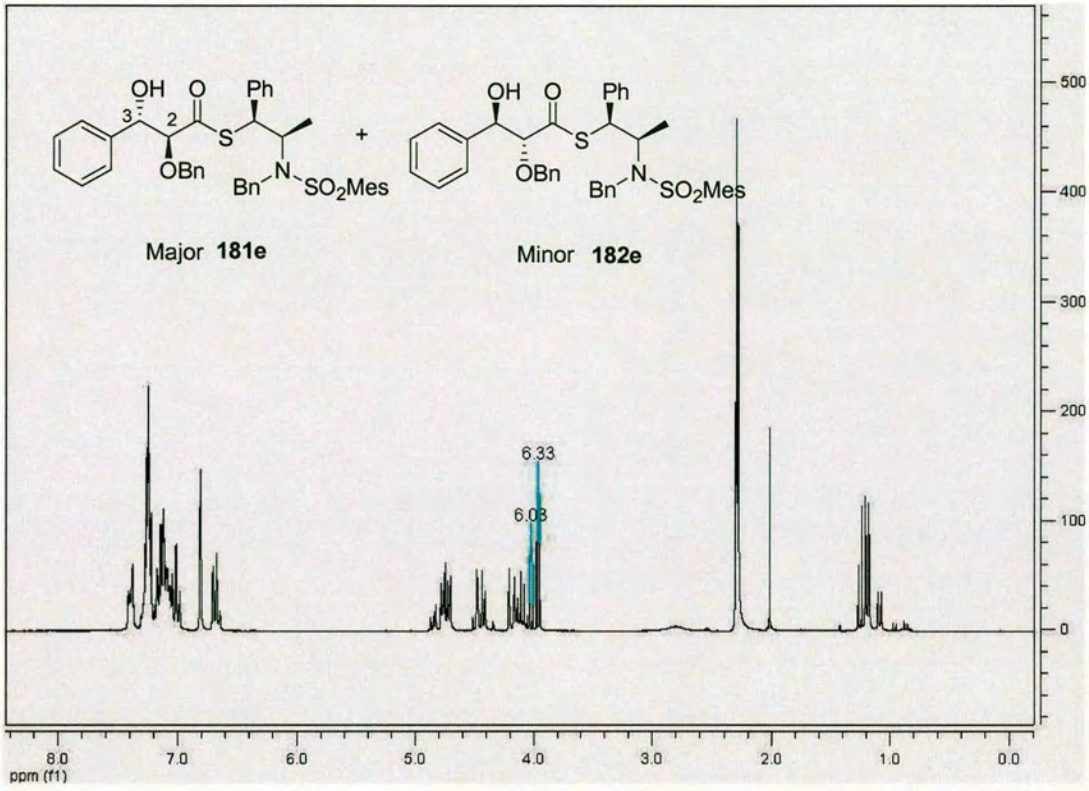
Table 13: Synthesis of *anti*-glycolate aldols. Reagents and conditions: a) c-Hex_2BCl (3.0 eq.), Base (2.5 eq.), Solvent, -78 °C, 1 h, then benzaldehyde (3.0 eq.), -78 °C, 2 h, 0 °C, 1.5 h. [b] by NMR and HPLC of diastereomeric mixture.

As shown in **table 13** *anti*-aldol products were obtained in very high *anti*:*syn* selectivities (from 94:6 to 99:1) independent of the base (Et_3N, $^iPr_2EtN$) or solvent (ether, CH_2Cl_2) used. In contrast, the *anti*:*anti* facial selectivity was found to be lower (from 71:29 to 77:23) although this ratio was not significantly dependent on either the base or solvent.

3.3.3 Assignment of Relative Stereochemistry

As described previously for the propionate and *syn*-glycolate aldols, the assignment of the relative stereochemistry was made on the basis of the coupling constant value between C2 and C3 protons in the aldol adducts generated (**figure 12**).

NMR analysis of the mixture of diastereoisomers **181e-182e** (**figure 24**) and the isolated major aldol-adduct **181e** (**figure 25**) allowed assignment of their *anti* stereochemistry. The coupling constant between the C2 and C3 protons of the major *anti* aldol **181e** was found to be around 6.4 Hz (**figures 24** and **25**) while it was 6.0 Hz for minor *anti* aldol adduct **182e** (**figure 24**), both higher values than those found for the Bn-protected *syn*1 (**171e**) and *syn*2 (**172e**) aldol adducts from benzaldehyde generated as described in **tables 10 and 12** (5.2 and 3.8 Hz respectively).



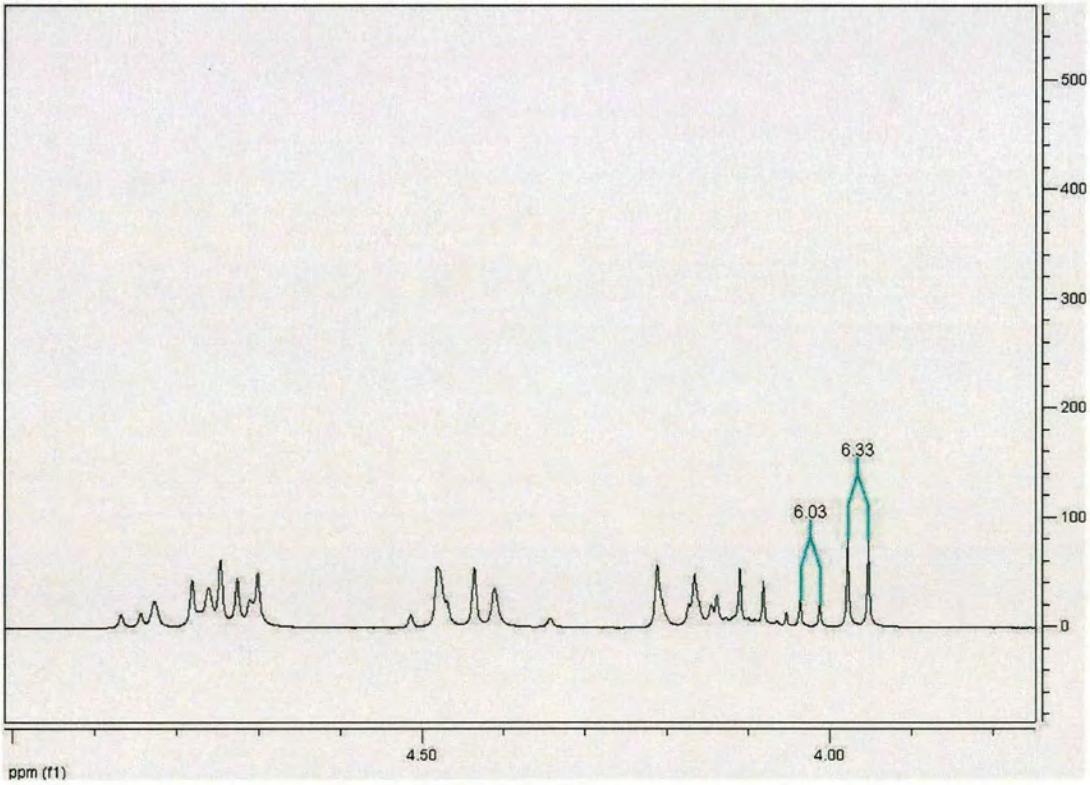
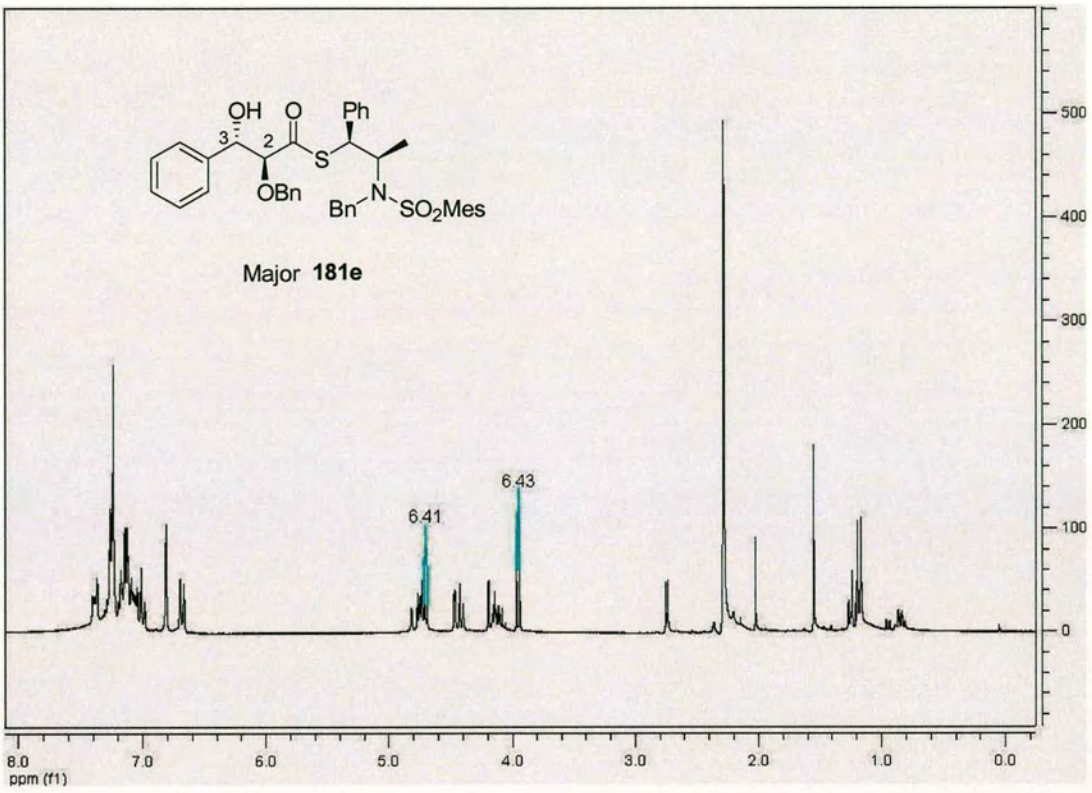


Figure 24: The NMR mixture of *anti*-aldol adducts **181e** and **182e** and its expansion, showing the coupling constants between C2 and C3 protons.



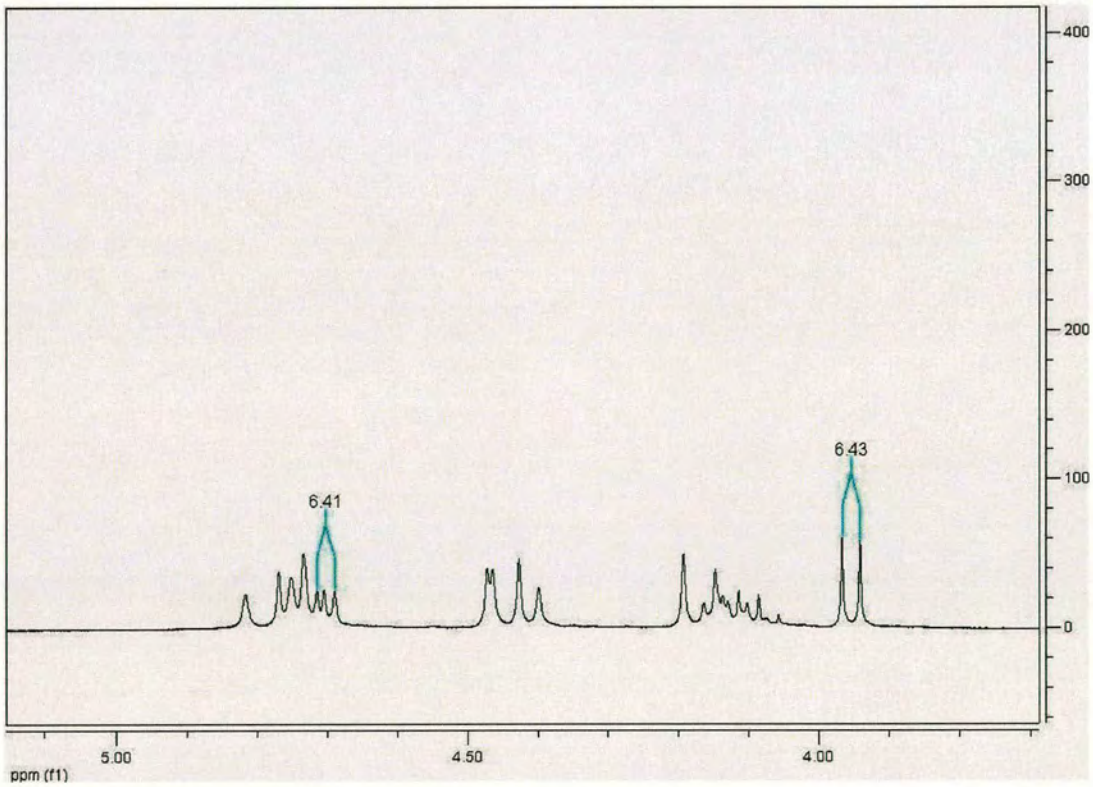
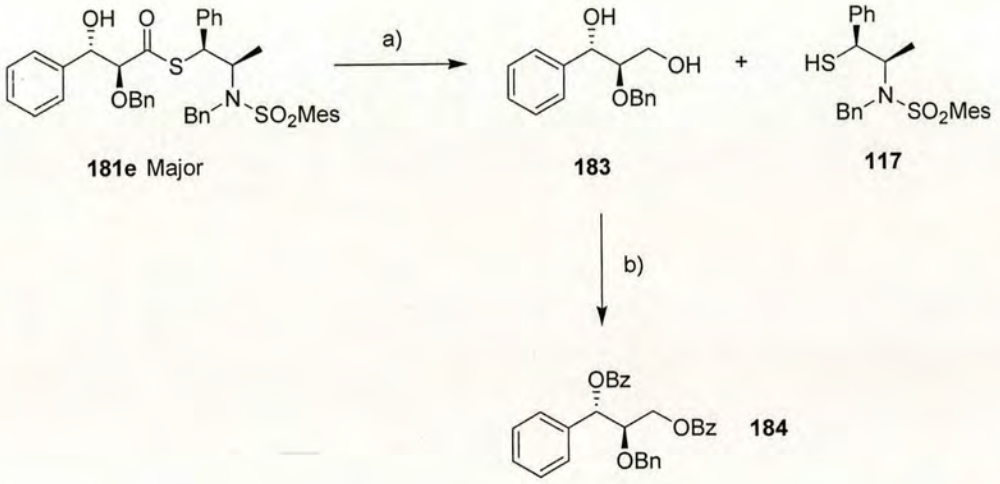


Figure 25: The NMR of major *anti*-aldol adduct **181e** and its expansion, showing the coupling constant between C2 and C3 protons.

3.3.4 Proof of Absolute Stereochemistry

The absolute stereochemistry of major *anti* aldol-adduct **181e** was proved by measurement of optical rotation value of derivative **184** (obtained by reduction of **181e** to diol **183** and subsequent benzoylation of **183** to give **184**), and its comparison with the literature (**scheme 55**).



$[\alpha]_D$ = - 30.4 / Lit.[139] $[\alpha]_D$ = - 31.6

Scheme 55: Synthesis and optical rotation value of **184**.[139] Reagents and conditions: a) $NaBH_4$ (10 eq.), THF(aq.), RT, 1 h (78% of **183**, 83% of **117**). b) Benzoyl chloride (4 eq.), DMAP (10 mol%), Py, RT, 14 h (96% of **184**).

The $[\alpha]_D$ obtained for **184** was in good agreement with the literature value,[139] demonstrating achievement of the same absolute stereochemistry with the thiol auxiliary **117** to that reported for the *anti* propionate aldol reaction with the Abiko-Masamune auxiliary.[30-34]

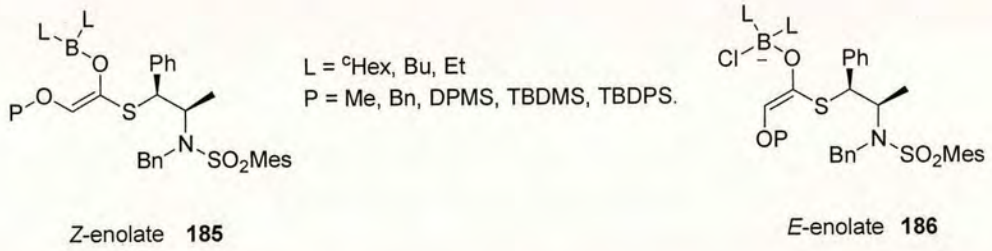
Having taken into account this result and that *syn* aldol adducts were generally present in less than 6% under all the conditions investigated, assignment of the absolute stereochemistry for the minor *anti* diastereoisomer and the *syn* aldol adducts was made on the basis of the Abiko-Masamune precedent.[30-34]

3.4 SYNTHESIS OF *SYN* SILYL ALDOLS

3.4.1 Preliminary Computational Studies

As described before, *syn*-glycolate aldols were synthesised in excellent *syn*:*anti* diastereoselectivities but in low *syn*:*syn* diastereofacialselectivity (**table 10**). In order to investigate ways to improve this moderate facial selectivity, modelling of the ground state conformations of the thiolester was performed using Gaussian at a semi-empirical level (AM1) *in vacuo*.

These preliminary computational studies of the ground state conformations of *E*- and *Z*-enolates of the glycolate thiolester using different ligands and protecting groups (**figure 26**), suggested that by using TBDPS as the protecting group rather than either Me or Bn, an increase in the facial selectivity could be possible by means of blocking one of the two faces of the enolate for the aldehyde approach (*E*-enolates formed with c-Hex_2BCl, have tetrahedral geometry and negatively charged B atom, *Z*-enolates formed with c-Hex_2BOTf, Bu_2BOTf or Et_2BOTf, are fully dissociated and have a trigonal planar neutral B atom) (**figure 26**).[12,140-141]



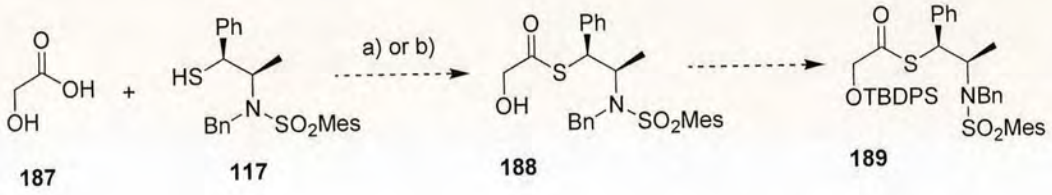
Z-enolate **185** *E*-enolate **186**

Figure 26: *Z*- and *E*-enolates modelled using Gaussian AM1 *in vacuo*.

Based on the results of these preliminary computational studies, we decided to investigate the selective glycolate aldol reaction of TBDPS-protected thiolesters.

3.4.2 Synthesis of TBDPS-Protected Thiolesters

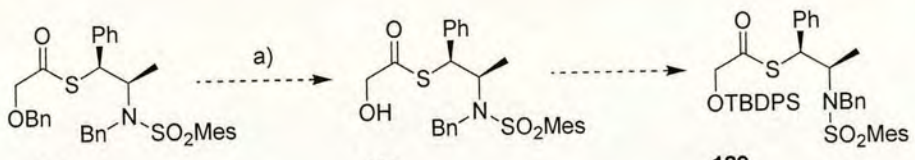
Several attempts to synthesise the TBDPS-protected thiolester **189** via the unprotected precursor **188** were undertaken. The initial approach involved coupling of glycolic acid **187** and thiol auxiliary **117** using coupling reagent DIC (*N,N*-diisopropylcarbodiimide) in the presence of catalytic DMAP in CH_2Cl_2, conditions previously used in the formation of Me- and Bn-protected thiolesters (**scheme 51**). The coupling reaction was also carried out using DSC (*N,N*-disuccinimidylcarbonate) in an attempt to avoid the urea side product generated with DIC. Unfortunately, under both sets of conditions only thiol auxiliary **117** was recovered and just traces of desired product **188** were observed. Failure in the production of thiolester **188**, probably due to polymerisation of glycolic acid under the coupling conditions, made the synthesis of TBDPS-protected **189** by this route impossible (**scheme 56**).



187 117 188 189

Scheme 56: Attempted coupling of glycolic acid and thiol auxiliary **117**. Reagents and conditions: a) **187** (1.0 eq.), **117** (1.1 eq.), DMAP (10 mol%), DIC (1.5 eq.), CH_2Cl_2, 10 min at 0 °C, overnight RT. b) **187** (1.0 eq.), Et_3N (1.1 eq.), DSC (1.5 eq.), DMF, 2 h, RT, then **117** (1.2 eq.), overnight RT.

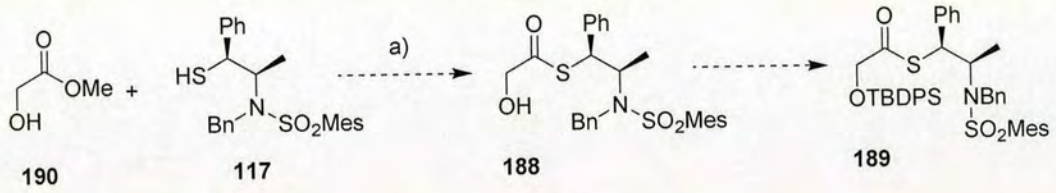
We also investigated the synthesis of **189** through unprotected thiolester **188**, via hydrogenolysis of benzyl-protected thiolester **166**, readily prepared by coupling of commercially available benzyloxyacetic acid and thiol **117** with coupling reagent DIC as described in **scheme 51**. Unfortunately, catalytic hydrogenolysis of **166** did not take place after 3 days and only traces of the desired product **188** were detected (**scheme 57**).



166 188 189

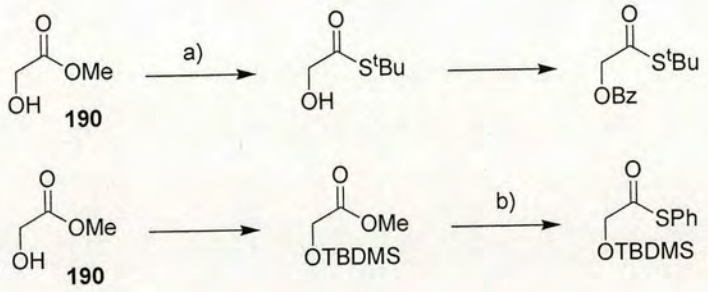
Scheme 57: Attempted synthesis of thiolester **188** via hydrogenolysis of **166**. Reagents and conditions: a) Pd/C, H_2, MeOH.

Gennari[142] has reported the synthesis of protected glycolate thiolesters from unprotected methyl glycolate by using the Lewis acid $AlMe_3$. Thus, we decided to investigate a different route towards **189** under Gen nari's Lewis acidic conditions. Unfortunately, repetition of the conditions used by Gennari failed to generate thiolester **188** from thiol auxiliary **117**, and only starting materials were recovered probably due to the use of a bulkier thiol (**scheme 58**).



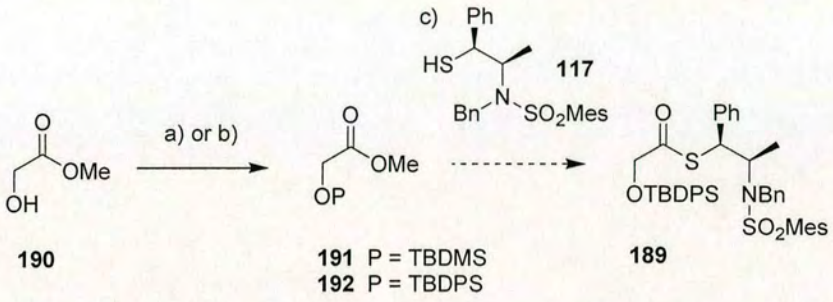
Scheme 58: Attempted synthesis of thiolester **188** from methyl glycolate **190**. Reagents and conditions: a) **117** (1.2 eq.), $AlMe_3$ (1.2 eq.), CH_2Cl_2, 30 min at 0 °C, then **190** (1.0 eq.), 1 h at 0 °C, overnight RT.

Although Gennari has reported the synthesis of protected glycolate thiolesters, through thiol addition to methyl glycolate and subsequent glycolate protection, prior TBDMS-protection of methyl glycolate followed by thiol addition proved to be more effective (53% of ^tBuSH addition to methyl glycolate with $AlMe_3$ in CH_2Cl_2, 79% of PhSH addition to TBDMS-protected methyl glycolate with $AlMe_3$ in CH_2Cl_2) (**scheme 59**).[142]



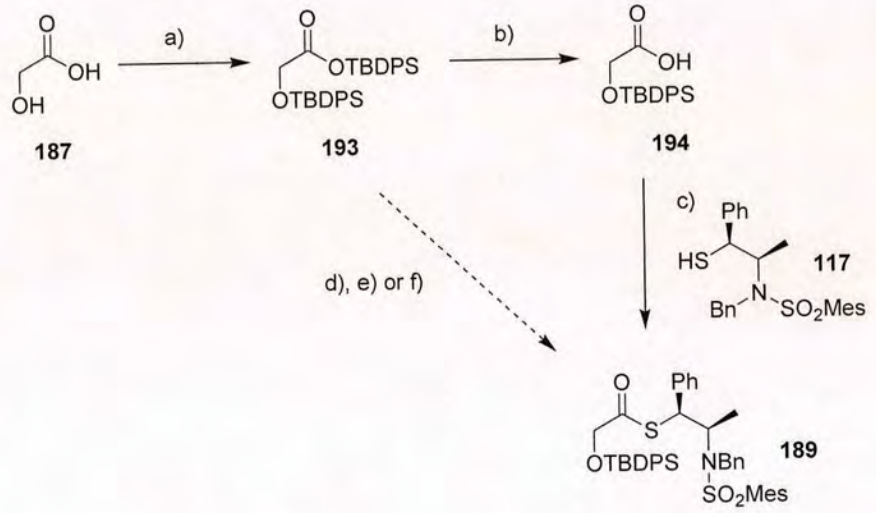
Scheme 59: Gennari's synthesis of protected glycolate thiolesters. Reagents and conditions: a) ^tBuSH, $AlMe_3$, CH_2Cl_2 (53%). b) PhSH, $AlMe_3$, CH_2Cl_2 (79%).

Thus, we decided to repeat these conditions with our thiol auxiliary **117**. Treatment of methyl glycolate with either TBDMSCl or TBDPSCl and imidazole in DMF, afforded TBDMS- and TBDPS-protected methyl glycolates in excellent yields. However, addition of thiol **117** to TBDPS-protected methyl glycolate **192** under Gennari's conditions,[142] failed to generate thiolester **189** and again only thiol auxiliary **117** was recovered (**scheme 60**).



Scheme 60: Attempted synthesis of thiolester **189** from TBDPS-protected methyl glycolate **192**. Reagents and conditions: a) **190** (1.0 eq.), imidazole (2.5 eq.), TBDMSCl (1.2 eq.), DMF, RT, 4 h (100%). b) **190** (1.0 eq.), imidazole (2.5 eq.), TBDPSCl (1.2 eq.), DMF, RT, 4 h (98%). c) **117** (2.0 eq.), $AlMe_3$ (2.0 eq.), CH_2Cl_2, 30 min at 0 °C, then **192** (1.0 eq.), 1 h at 0 °C, overnight RT.

However, a three-step high yielding route (81% overall yield) proved to be successful in the synthesis of TBDPS-protected glycolate thiolester **189**. Hydrolysis of TBDPS-ester **193** (derived from glycolic acid **187**) with K_2CO_3 in THF/MeOH/H_2O afforded acid **194** in very good yield in just 30 min.[143] Glycolate acid **194** was immediately coupled with thiol auxiliary **117** using coupling reagent DIC in the presence of catalytic DMAP, in excellent yield (**scheme 61**). Although some instability of glycolate acid **194** was detected, its immediate use after flash chromatography purification proved to be successful in the synthesis of thiolester **189** (98% when used inmediately, no reaction when acid **194** was used after one day).

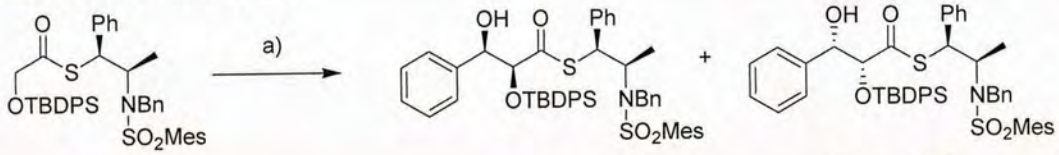


Scheme 61: Synthesis of thiolester **189**. Reagents and conditions: a) **187** (1.0 eq.), TBDPSCl (4.0 eq.), py, 3.5 h, RT (95%). b) **193** (1.0 eq.), K_2CO_3 (3.0 eq.), THF/MeOH/H_2O 1:2:1, 30 min, RT (86%).[143] c) **117** (1.0 eq.), **194** (2.3 eq.), DMAP (10 mol%), DIC (2.0 eq.), CH_2Cl_2, 30 min at 0 °C, overnight RT (98%). d) **117** (1.2 eq.), NaH (1.2 eq.), DMF, 30 min at 0 °C, then **193** (1.0 eq.), 1 h at 0 °C, 1 h RT. e) **117** (1.2 eq.), K_2CO_3 (1.2 eq.), THF, 30 min at 0 °C, then **193** (1.0 eq.), 1 h at 0 °C, overnight RT. f) **117** (1.2 eq.), $AlMe_3$ (1.2 eq.), CH_2Cl_2, 30 min at 0 °C, then **193** (1.0 eq.), 1 h at 0 °C, overnight RT.

A more direct route towards the synthesis of **189** involved the addition of thiol auxiliary **117** to TBDPS-ester **193**. Although three different sets of conditions were investigated, none of them afforded the desired product. Use of NaH in DMF produced degradation of the thiol, suggesting the instability of **117** under basic conditions. Use of a milder base, such as K_2CO_3, failed to afford the addition and mainly thiol auxiliary **117** was recovered together with some traces of decomposed thiol. Finally, $AlMe_3$ was also inefficient and only starting material was recovered (**scheme 61**).

3.4.3 Synthesis of TBDPS-Protected *Syn* Glycolate Aldols

With an efficient synthetic strategy towards the TBDPS-protected glycolate thiolester **190** in hand (**scheme 56**), we decided to investigate the potential influence that the TBDPS group could have in the improvement of the diastereofacial selectivity of the *syn* glycolate aldol reaction. Thus, initial studies involving the aldol reaction between thiolester **190** and benzaldehyde, in the presence of different combinations of boron-triflate/chloride and bases were undertaken (**table 14**). As described previously for the Me- and Bn-protected glycolate esters (**table 10**), the use of boron-triflate/base always afforded *syn*-glycolate products whilst the use of c-Hex_2BCl/base gave *anti*-glycolate aldols. Interestingly, use of either triflate (entries 1 and 4, **table 14**) or chloride (entry 2, **table 14**) in the silyl aldol reaction always afforded *syn*-glycolate products. Additionally, the use of different ligand sizes on the triflate (entry 1 *vs* entry 4, **table 14**) did not result in inversion of the facial selectivity as previously observed with the Me- and Bn-protected glycolate aldols (**table 10**). In contrast, the stereochemistry of the major and minor aldol adducts was constant, independent of the conditions used (**table 14**).



190 Major **195e** Minor **196e**

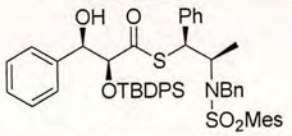
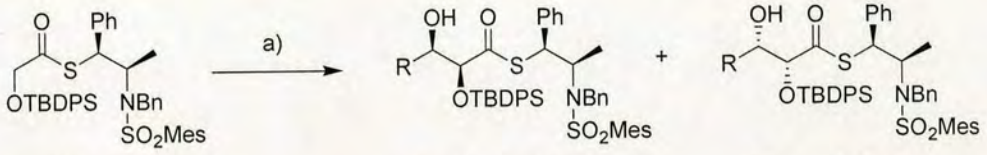
		
Entry	Triflate / Base	Yield (%) / ds (*syn* : *syn*) // ds (*syn* : *anti*)[b]
1	(^{c}Hex)$_2$BOTf / Et_3N	82 (92 : 8) // (99 : 1)
2	(^{c}Hex)$_2$BCl / Et_3N	95 (90 : 10) // (99 : 1)
3	Bu_2BOTf / Et_3N	no reaction
4	Bu_2BOTf / $^i Pr_2EtN$	77 (61 : 39) // (99 : 1)

Table 14: Synthesis of *syn*-silyl glycolate aldols under different conditions. Reagents and conditions: a) boron-triflate or chloride (3 eq.), base (2.5 eq.), CH_2Cl_2, 1 h, -78 °C; then benzaldehyde (3.0 eq.), 2 h, -78 °C, 1.5 h, 0 °C. [b] by NMR and HPLC of diastereomeric mixture.

Analysis of the results described in **table 14** showed an important improvement in the facial selectivity due to the presence of bulky TBDPS-group. Although Bu_2BOTf/Et_3N (entry 3, **table 14**) failed to produce aldol adducts and $Bu_2BOTf/^iPr_2NEt$ (entry 4, **table 14**) gave low facial selectivity (similar results have been reported by Andrus[65] in the *syn*-selective aldol reaction with Bn-protected esters, where Bu_2BOTf/Et_3N failed to give aldols and $Bu_2BOTf/^iPr_2NEt$ only produced 75:25 *syn*:*syn* selectivity). In contrast, Hex_2BCl and c-Hex_2BOTf with Et_3N afforded *syn*-aldol adducts in high yields and excellent diastereoselectivities (*syn*:*anti* > 99:1, *syn*:*syn* > 90:10, entries 1 and 2, **table 14**). Encouraged by these results, we decided to investigate the use of our optimised conditions (c-Hex_2BOTf/Et_3N, entry 1, **table 14**) with a range of aldehydes, in order to prove the generality of the reaction conditions (**table 15**).



190 Major **195a,c-e** Minor **196a,c-e**

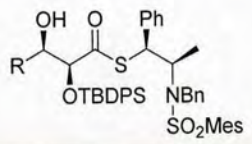
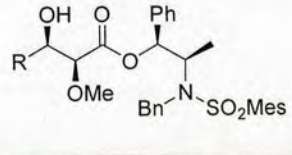
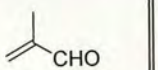
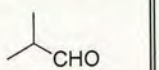
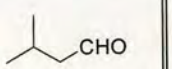
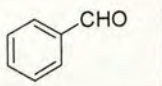
			
Aldehyde		Yield (%) / ds (*syn* : *syn*)[b]	Yield (%) / ds (*syn* : *syn*)
a		76 (92 : 8)	76 (96 : 4)[65]
c		73 (95 : 5)	88 (96 : 4)[65]
d		64 (95 : 5)	92 (93 : 7)[65]
e		82 (92 : 8)	87 (97 : 3)[65]

Table 15: Synthesis of *syn*-silyl glycolate aldols with a range of aldehydes in high yields and excellent diastereoselectivities. Reagents and conditions: a) c-Hex_2BOTf (3 eq.), Et_3N (3.0 eq.), CH_2Cl_2, 1 h, -78 °C, then aldehyde (3.0 eq.), 2 h, -78 °C, 1.5 h, 0 °C. [b] by NMR and HPLC of diastereomeric mixture.

As shown in **table 15** excellent diastereoselectivities were obtained with a range of aldehydes (*syn*:*anti* > 99:1, *syn*:*syn* > 92:8), demonstrating the generality of the reaction conditions. The results obtained for our *syn*-silyl glycolate aldols were comparable to those reported by Andrus[65] for the *syn*-selective glycolate aldol reaction of Abiko-Masamune esters (*syn*:*syn* > 93:7) (**table 15**). Interestingly, TBDPS-protected Abiko-Masume esters failed to generate aldol products even when c-Hex_2BOTf/ Et_3N were used over extended times and at warmer temperatures.[65]

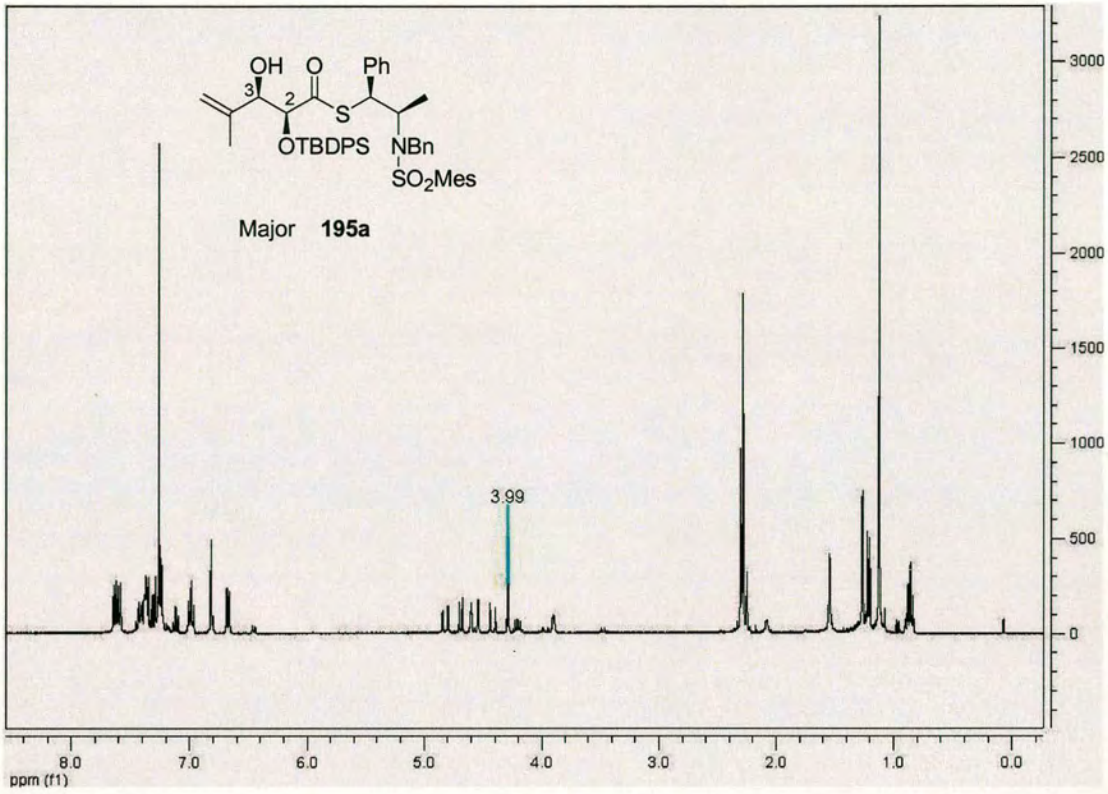
3.4.4 Assignment of Relative and Absolute Stereochemistry

As described in sections 2.2.2, 3.2.2 and 3.3.3 with the propionate and Me- and Bn-protected glycolate aldol adducts, assignment of the *syn* relative stereochemistry of the TBDPS-protected glycolate products was made on the basis of coupling constant value between C2 and C3 protons in the aldol adducts generated (**figure 12**).

Major and minor aldol adducts **195e** and **196e** from benzaldehyde were shown to have typical *syn* coupling constant values by NMR analysis of the crude mixture of diastereoisomers (4.4 and 3.9 Hz, respectively).

Similarly, NMR analysis of major aldol adducts **195a** from methacrolein (**figure 27**), **195c** from isobutyraldehyde (**figure 28**), and **195d** from isovaleraldehyde, also showed *syn* coupling constant values (4.0, 3.5 and 3.2 Hz, respectively).

Assignment of the absolute stereochemistry was made on the basis of the stereochemical outcome of the reaction previously proved in sections 3.2.3 and 3.3.4 for the *syn* Me-protected and the *anti* Bn-protected glycolate aldol adducts, which was also shown to be in good agreement with the absolute stereochemistry reported for the Masamune oxygenated version.[65]



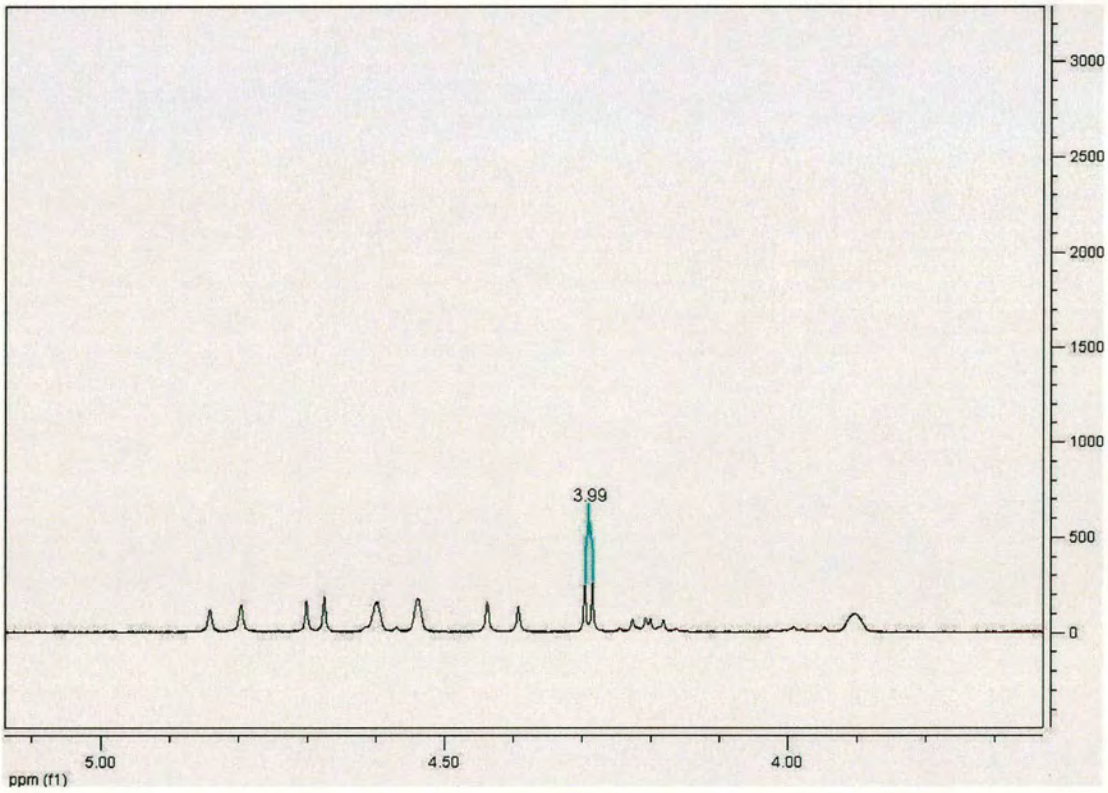


Figure 27: The NMR of *syn*-aldol adduct **195a** and its expansion, showing the coupling constant between C2 and C3 protons.

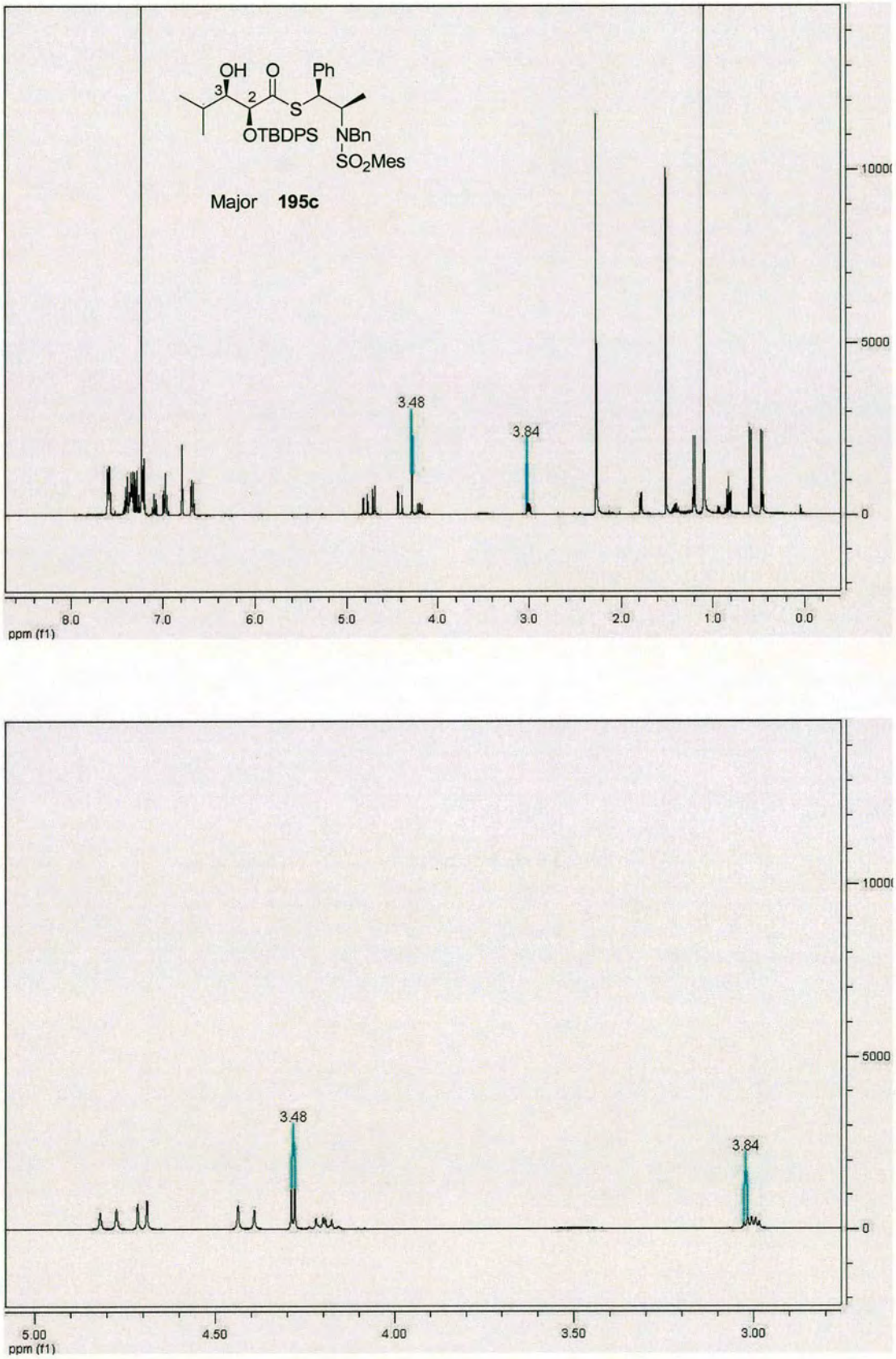
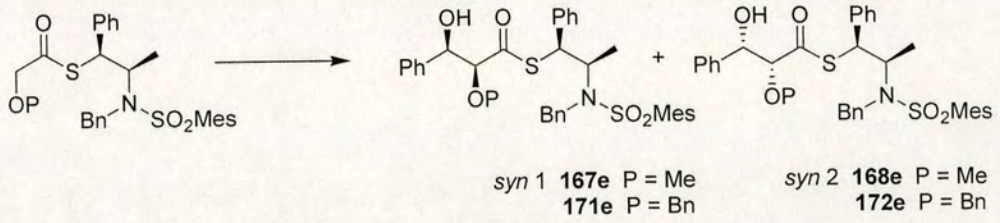


Figure 28: The NMR of *syn*-aldol adduct **195c** and its expansion, showing the coupling constant between C2 and C3 protons.

3.5 CONCLUSION

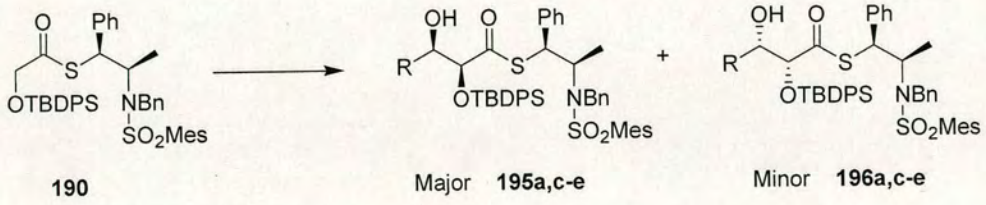
3.5.1 Synthesis of *Syn* Glycolate Aldols

Me- and Bn-protected *syn* glycolate aldol adducts (**scheme 62**) were synthesised in excellent *syn*:*anti* diastereoselectivity (> 91:9) and moderate *syn*:*syn* diastereofacial selectivity (no higher than 21:79; **table 10**).



Scheme 62: Synthesis of Me- and Bn-protected *syn* glycolate aldols.

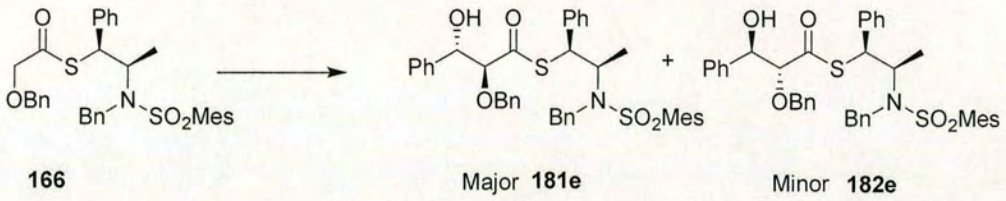
Improvement of the diastereofacial selectivity was achieved using the TBDPS protecting group. In this manner, TBDPS-protected *syn* glycolate aldol adducts (**scheme 63**) were synthesised in excellent *syn*:*anti* diastereoselectivity (> 98:2) and high *syn*:*syn* facial selectivity (> 92:8; **table 15**).



Scheme 63: Synthesis of TBDPS-protected *syn* glycolate aldols.

3.5.2 Synthesis of *Anti* Glycolate Aldols

Anti glycolate aldol adducts (**scheme 64**) were synthesised in excellent *anti*:*syn* diastereoselectivity (> 94:6) and moderate *anti*:*anti* diastereofacial selectivity (from 71:29 to 77:23; **table 13**).



166 Major **181e** Minor **182e**

Scheme 64: Synthesis of *anti* glycolate aldols.

3.5.3 Proof of Relative and Absolute Stereochemistry

The relative stereochemistry of *syn* and *anti* aldol adducts was assigned by NMR analysis of coupling constants between vicinal protons.

The absolute stereochemistry was proved by X-ray analysis or optical rotation values of different derivatives, and their agreement with the literature precedent.

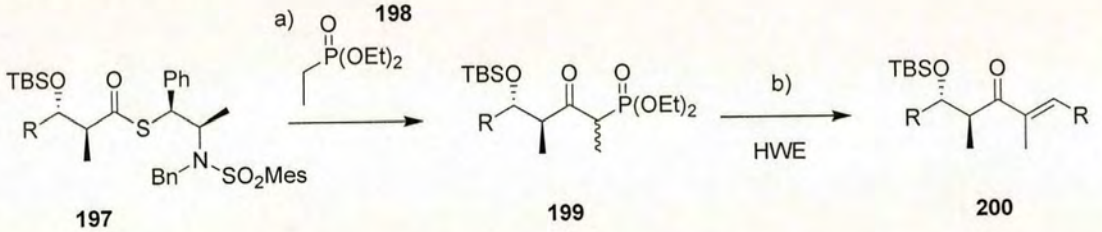
CHAPTER 4: RESULTS AND DISCUSSION 3

4.1 DEVELOPMENT OF MILD DISPLACEMENT CONDITIONS

As discussed in chapter 1, the main focus for the development of the thiol auxiliary **117** was its potentially facile displacement with a range of nucleophiles under very mild conditions. Thus, we decided to investigate the auxiliary removal under a variety of useful reaction conditions in synthesis.

4.1.1 Phosphonate Displacement Precedent

Previous studies carried out within the Hulme group[91] proved the efficient displacement of the auxiliary by phosphonate nucleophiles, which could then allow direct extension of the aldol adduct using a Horner-Wadsworth-Emmons reaction[144] (HWE) (**table 16**).



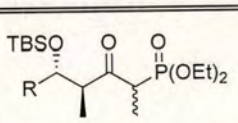
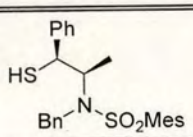
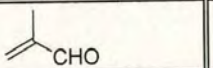
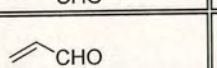
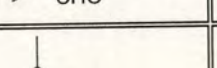
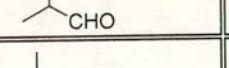
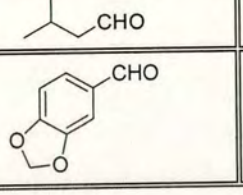
		
Aldehyde	Yield (%)	Yield (%)
	81	85
	90	91
	89	85
	91	79
	78	80

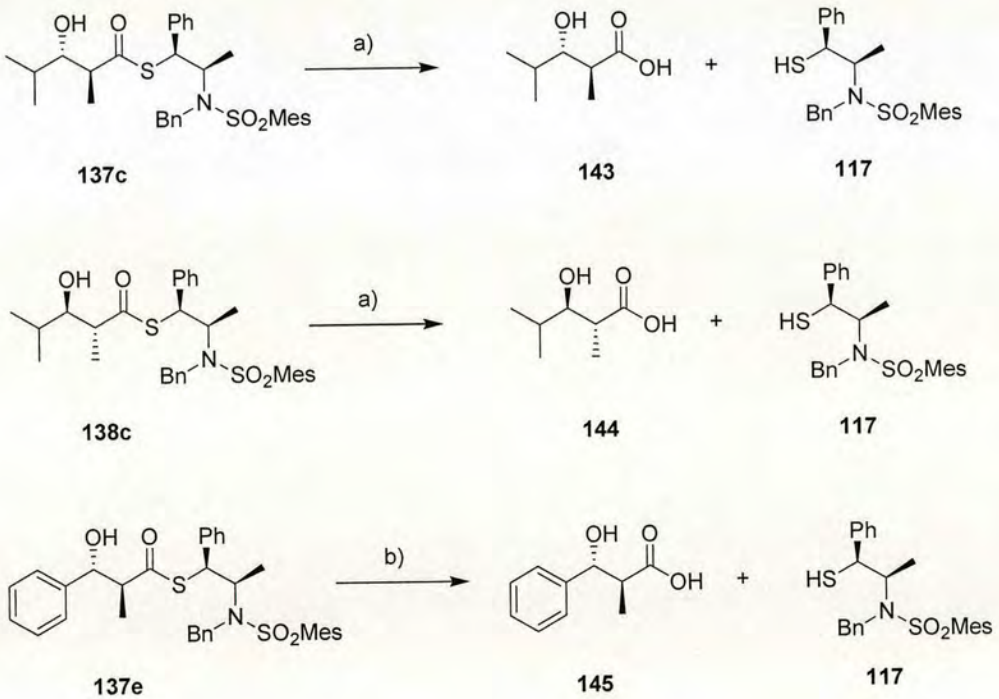
Table 16: Phosphonate displacement. Reagents and conditions: a) **198**, BuLi, THF, -78 °C. b) RCHO, $Ba(OH)_2$, THF (aq.), 0 °C.[91]

As shown in **table 16** treatment of protected aldol adducts **197** with the lithium anion of diethyl ethane phosphonate **198** afforded the desired phosphonate esters **199** in high yields (> 81%). In all cases the thiol auxiliary **117** was also recovered in good yield (> 79%). Phosphonate esters **199** were then treated under standard conditions for the Horner-Wadsworth-Emmons reaction to generate alkenes **200**.

After the successful displacement of auxiliary **117** was achieved with a phosphonate anion, we decided to investigate the displacement reaction with other mild nucleophiles.[92]

4.1.2 Hydrolysis Reaction

Initially we decided to investigate the hydrolysis reaction of our thiolester aldol adducts; corresponding reactions of ester aldol adducts have been shown to be quite sluggish with the Masamune auxiliary.



Scheme 65: Hydrolysis of *anti*-propionate aldol adducts. Reagents and conditions: a) LiOH (3.0 eq.), THF/H_2O (2:1), RT, 30 min (88% of **143**; **117** recovered in 99%), (86% of **144**; **117** recovered in 88%). b) LiOH (20 eq.), THF/H_2O (2:1), RT, 20 min (98% of **145**, 89% of **117**).

As shown in **scheme 65** treatment of *anti*-propionate aldol adducts **137c** and **138c** with LiOH in THF/H_2O (2:1), afforded acids **143** and **144** after just 30 minutes in excellent yield (> 86%). When the reaction was carried out with aldol-adduct **137e** in a smaller scale, an increase in the number of equivalents of LiOH was used (20 eq. instead of 3.0 eq.), producing acid **145** after just 20 minutes in 98%.

In contrast, LiOH-mediated hydrolysis of the Abiko-Masamune auxiliary has been reported to require much longer reaction times,[66,145] typically between 24-48 h. Thus, the results described above demonstrate the facile hydrolysis of the thiol auxiliary **117** compared to its Abiko-Masamune oxygenated counterpart. Furthermore, in all cases the thiol auxiliary **117** was recovered in high yield (> 88%), allowing its subsequent use in other reactions.

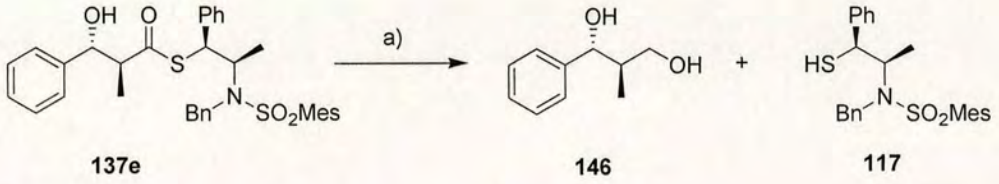
The synthesis of acids **143**, **144** and **145** permitted assignment of absolute stereochemistry of the propionate aldol adducts by optical rotation analysis. The $[\alpha]_D$ calculated were in good agreement with the literature values, as previously shown in **schemes 43** and **44**.

When the hydrolysis reactions were left for extended time periods (1-14 h), partial degradation of the chiral auxiliary **117** was observed, suggesting instability of the thiol under strong basic conditions, as previously observed in **schemes 56** and **59** in the presence of NaH.

The attempted hydrolysis of aldol adducts under extremely mild conditions using K_2CO_3 in aqueous THF, failed to produce acid products and only starting material was recovered after 14 h.

4.1.3 Reduction to Alcohol

After the successful hydrolysis reaction, we examined the reduction of aldol adducts to alcohols, a reaction which typically requires rather harsh conditions ($LiAlH_4$, DIBAL) with the Abiko-Masamune auxiliary.[45,146-148] In contrast, we found that upon treatment of aldol-adduct **137e** with $NaBH_4$, diol **146** and chiral auxiliary **117** were obtained in excellent yield after just 1 h (99% and 83% respectively) (**scheme 66**).

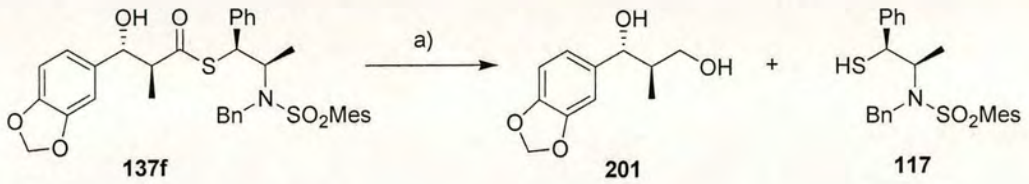


137e **146** **117**

Scheme 66: Synthesis of diol **146** under mild reduction conditions. Reagents and conditions: a) $NaBH_4$ (10 eq.), THF(aq.), RT, 1 h (99% of **146**, 83% of **117**).

Synthesis of diol **146** allowed the absolute stereochemistry of aldol-adduct **137e** to be proved by optical rotation analysis, as previously shown in **scheme 45**.

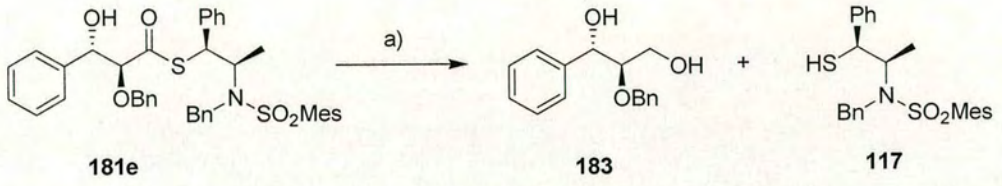
Similar conditions to those used with aldol-adduct **137e** were employed with *anti*-propionate aldol adduct **137f**, to generate its diol product **201** in 94% (auxiliary recovered in 88%) (**scheme 67**), confirming the efficiency of the mild reduction conditions for the removal of thiol auxiliary **117**.



137f **201** **117**

Scheme 67: Synthesis of diol **201** under mild reduction conditions. Reagents and conditions: a) $NaBH_4$ (50 eq.), THF(aq.), RT, 14 h (94% of **201**, 88% of **117**).

Glycolate *anti* aldol-adduct **181e** was also reduced to diol **183** in excellent yield (78%, auxiliary recovered in 83%) under the same conditions previously used with propionate aldol adducts **137e** and **137f** (**scheme 68**).



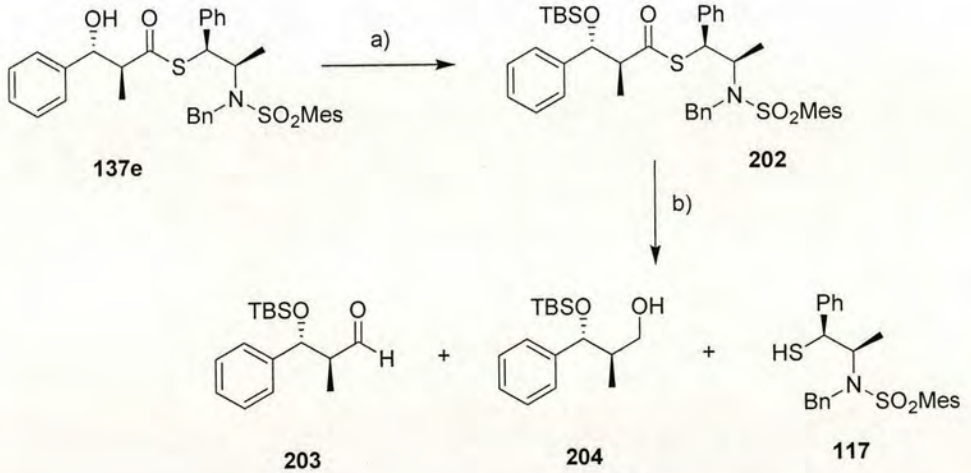
181e **183** **117**

Scheme 68: Synthesis of diol **183**. Reagents and conditions: a) $NaBH_4$ (10 eq.), THF(aq.), RT, 1 h (78% of **183**, 83% of **117**).

4.1.4 Reduction to Aldehyde

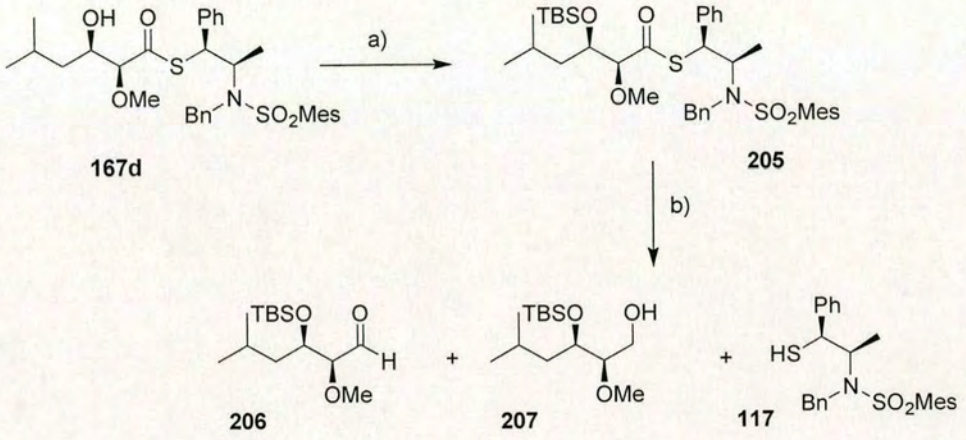
The direct reduction of aldol adducts to aldehydes using mild reductive conditions was achieved in moderate yield. Initial treatment of different unprotected aldol adducts with DIBAL at -78 °C failed to produce aldehydes, instead unreacted aldol adduct (46%) and a complex mixture of products (34%) were detected. Similar problems have been reported for the direct cleavage of Evan's oxazolidinones,[149] suggesting that protection of the free hydroxyl group was required.

Thus, protection of aldol adduct **137e** with TBSOTf and 2,6-lutidine followed by DIBAL reduction, afforded a crude mixture of thiol auxiliary **117** and aldehyde **203**. Unfortunately, the desired aldehyde **203** appeared to decompose when subjected to flash chromatography and only 13% was recovered probably due to a competing elimination reaction. Chiral auxiliary **117** was obtained in 84% and only traces of the alcohol product **204** were observed (**scheme 69**).



Scheme 69: Reduction of TBS-protected aldol **200** to aldehyde **201**. Reagents and conditions: a) TBSOTf (2.3 eq.), 2,6-lutidine (3.1 eq.), CH_2Cl_2, 0 °C, 2 h (88% brsm). b) DIBAL (2.0 eq.), CH_2Cl_2, -78 °C, 2 h (13% of **203**, 84% of **117**).

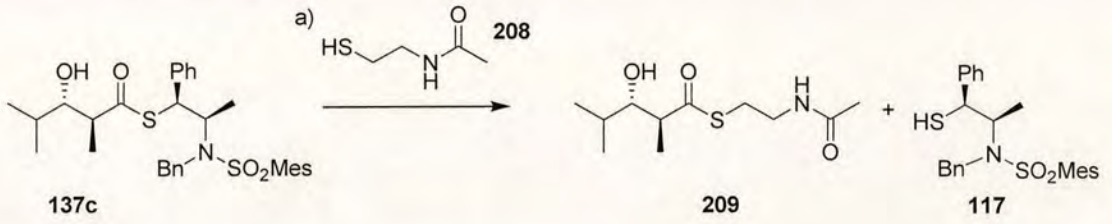
To avoid the undesired elimination reaction, the saturated TBS-protected aldol adduct **205** was treated under the same reductive conditions, to afford a 1:1 crude mixture of thiol auxiliary **117** and aldehyde **206**, which after flash chromatography purification gave aldehyde **206** in 53%. Despite the moderate yield only traces of unreacted aldol adduct and alcohol product **207** were observed, suggesting degradation of the aldehyde during the purification process (**scheme 70**).



Scheme 70: Reduction of TBS-protected aldol **205** to aldehyde **206**. Reagents and conditions: a) TBSOTf (2.6 eq.), 2,6-lutidine (3.0 eq.), CH_2Cl_2, 0 °C, 2 h (90% brsm). b) DIBAL (4.4 eq.), CH_2Cl_2, -78 °C, 2 h (53% of **206**, 71% of **117**).

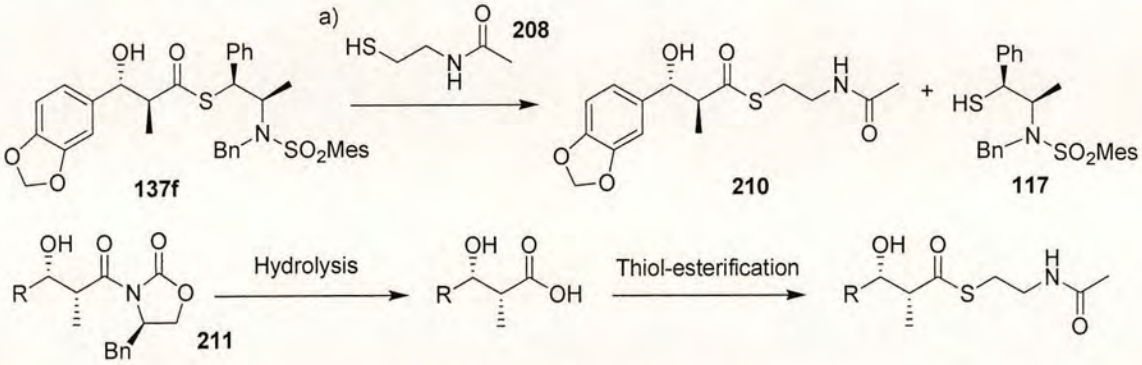
4.1.5 Transthiolesterification Reaction

It is known that *N*-acetylcysteamine (SNAc) thiolester derivatives are accepted as substrates by some polyketide[151-153] and nonribosomal peptide[154] synthases. When SNAc derivatives are used for feeding experiments, these unusual precursors are recognised as Acyl-S-CoA substitutes. Thus, the transthiolesterification reaction takes place next, and the desired precursor is loaded into the biosynthetic machinery. Having this in consideration the direct construction of SNAc thiolesters could be of high interest in synthesis. Therefore, transthiolesterification of aldol adduct **137c** was carried out under the extremely mild conditions reported by Raines (**scheme 71**).[155]



Scheme 71: Transthiolesterification of aldol **137c** to SNAc thiolester **209**. Reagents and conditions: a) *N*-acetylcysteamine **208** (15 eq.), $^{i}Pr_2NEt$ (15 eq.), DMF, RT, 1 h (88% of **209**, 93% of **117**).

Treatment of propionate aldol adduct **137c** with *N*-acetylcysteamine (SNAc) **208** in the presence of $^{i}Pr_2EtN$, gave SNAc thiolester **209** in only 1 h and in excellent yield (88%) (**scheme 71**). Treatment of aldol adduct **137f** under the same conditions afforded SNAc thiolester **210** in high yield, demonstrating the generality of the reaction conditions. This procedure is notable as it avoids the need for a two-step hydrolysis-thiolesterification process, which is typically used in the case of polyketide starter units derived from the Evans oxazolidinone (**scheme 72**).[156-158]

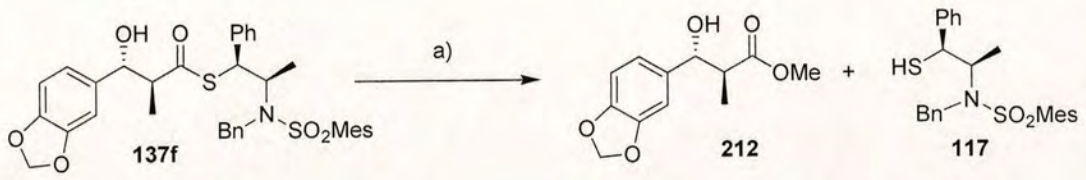


Scheme 72: SNAc thiolester formation from aldol adduct **137f** and Evans' aldol adduct **211**. Reagents and conditions: a) **208** (15 eq.), $^{i}Pr_2NEt$ (15 eq.), DMF, RT, 1 h (86% of **210**, 77% of **117**).

Attempted transthiolesterification under the conditions reported by Willis[159] (*N*-acetylcysteamine, Me_3Al, THF, 0°C) failed to produce the desired product and only complex mixtures were obtained, including the products of elimination and retroaldol reaction.

4.1.6 Transesterification Reaction

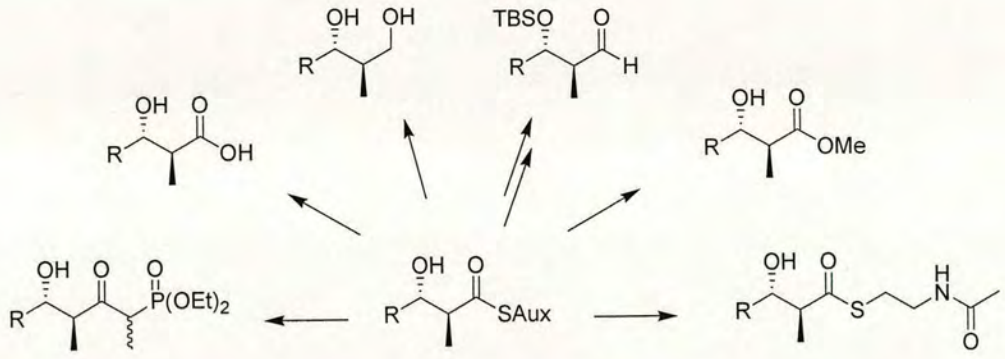
Finally, transesterification[160] of aldol adduct **137f** was readily achieved by treatment with sodium methoxide in methanol, giving methyl ester **212** in 94% after just 30 minutes. Auxiliary **117** was also recovered in excellent yield (99%) (**scheme 73**).



Scheme 73: Transesterification reaction of aldol adduct **137f** to give methyl ester **212**. Reagents and conditions: a) NaOMe (2.0 eq.), MeOH, RT, 30 min (94% of **212**, 99% of **117**).

4.2 CONCLUSION

We have demonstrated the facile displacement of chiral auxiliary **117** with a range of nucleophiles under very mild conditions, to give the corresponding phosphonate esters, acids, alcohols, aldehydes, methyl esters and SNAC thiolesters (**scheme 74**).



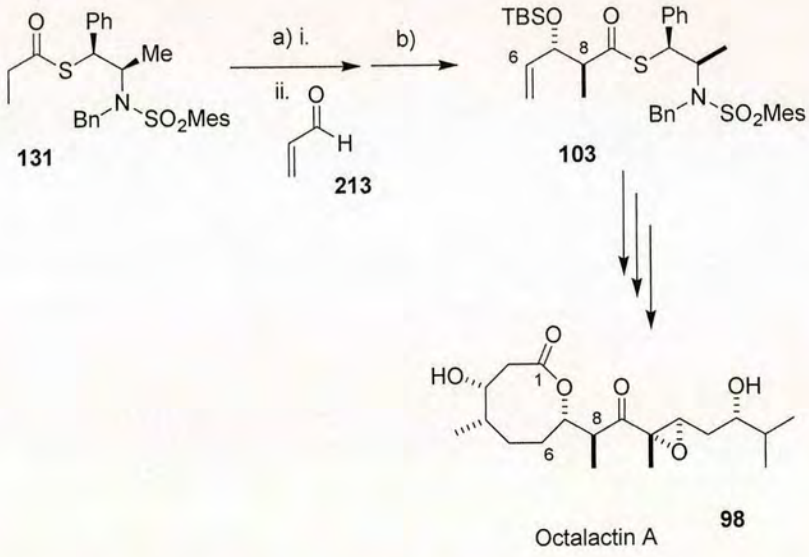
Scheme 74: Removal of thiol auxiliary **117** under a range of mild reaction conditions.

CHAPTER 5: FUTURE WORK

5.1 FUTURE WORK

5.1.1 Use of Thiol Auxiliary 117 in Natural Product Synthesis

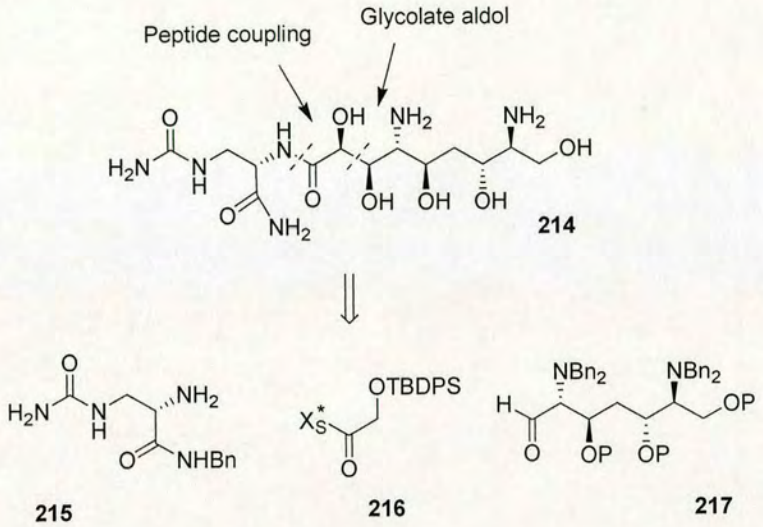
The new thiol auxiliary **117** has been successfully used in the Hulme group for an *anti*-selective boron-mediated propionate aldol reaction, in the route towards the synthesis of marine metabolite octalactin A **98**, achieving high yield (92%) and diastereoselectivity (*anti*:*anti* = 93:7) (**scheme 75**).[74] These results confirmed the high levels of diastereoselectivity showed by the auxiliary with a range of aldehydes for the *anti*-selective propionate aldol reaction (**table 2**),[91] making it an attractive alternative in synthesis to the Abiko-Masamune auxiliary.



Scheme 75: Use of the sulfur analogue of the Abiko-Masamune auxiliary in an *anti*-selective propionate aldol reaction towards the synthesis of octalactin A. Reagents and conditions: a) i. c-Hex_2BOTf, Et_3N, CH_2Cl_2, -78 °C; ii. **213**, -78 °C to 0 °C (92%, ds = 93:7). b) TBSOTf, 2,6-lutidine, CH_2Cl_2 (94%).[74]

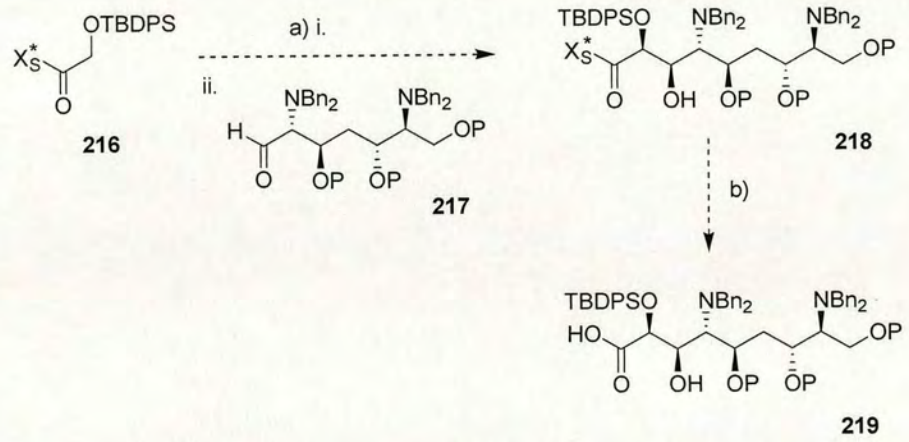
The selective glycolate aldol reaction using thiol auxiliary **117** has also been of high interest in our research. As described before, several studies were undertaken leading to the development of the optimised conditions to afford *syn* glycolate aldols in excellent diastereoselectivity (**table 15**). Thus, an extension of this investigation will include the use of this new glycolate-aldol methodology in natural product synthesis.

Investigations towards the synthesis of the aminopolyol antibiotic zwittermicin A **214** have been previously carried out in the Hulme group.[161] In these studies, a synthetic route involving a *syn*-selective glycolate aldol reaction followed by peptide bond formation was considered (**scheme 76**).



Scheme 76: Retrosynthetic analysis of zwittermicin A.[161]

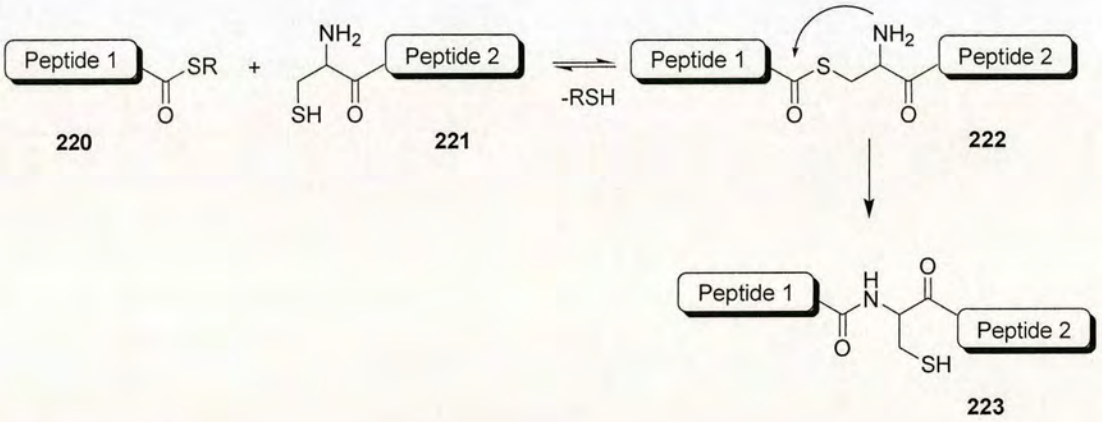
In the proposed synthetic route described above, our new aldol methodology could be used in the glycolate aldol reaction between TBDPS-protected thiolester **216** and aldehyde **217** (**scheme 77**).



Scheme 77: Proposed *syn*-selective glycolate aldol reaction towards zwittermicin A. Reagents and conditions: a) i. c-Hex_2BOTf, Et_3N, CH_2Cl_2; ii. **217**. b) LiOH, THF/H_2O, RT.

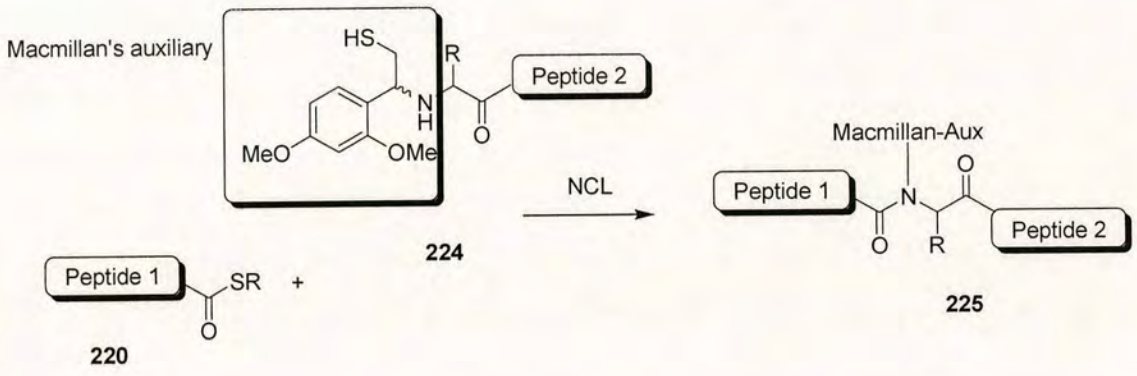
In this manner, fragment **218** could be generated in expected high yield and diastereoselectivity, and then used in the synthesis of zwittermicin A by hydrolysis (using the optimised hydrolysis conditions previously described in **scheme 65**) and subsequent peptide bond formation between acid **219** and nitrogen-rich fragment **215**.[162]

The peptide bond formation[163-165] between fragments **219** and **215** could be achieved using well-known coupling reagents such us: EDCI, DCC or DIC, in a similar way to that described in **scheme 51**. Alternatively, peptide bond formation could also be obtained via Native Chemical Ligation (NCL).[166,167] The method of NCL was first introduced by Kent[168] and is based on the reaction between a thiolester and the sidechain of a Cys residue. In this reaction, two fully unprotected peptides react to form an amide bond in aqueous conditions at neutral pH. The first step of this process involves the reversible chemoselective transthiolesterification of an unprotected peptide-α-thiolester **220**, with another unprotected peptide segment **221** containing an N-terminal Cys residue. The thiolester-linked intermediate **222** formed in this first step, spontaneously undergoes a rapid S→N-acyl transfer to form a native peptide bond at the ligation site (**scheme 78**).[166-177]



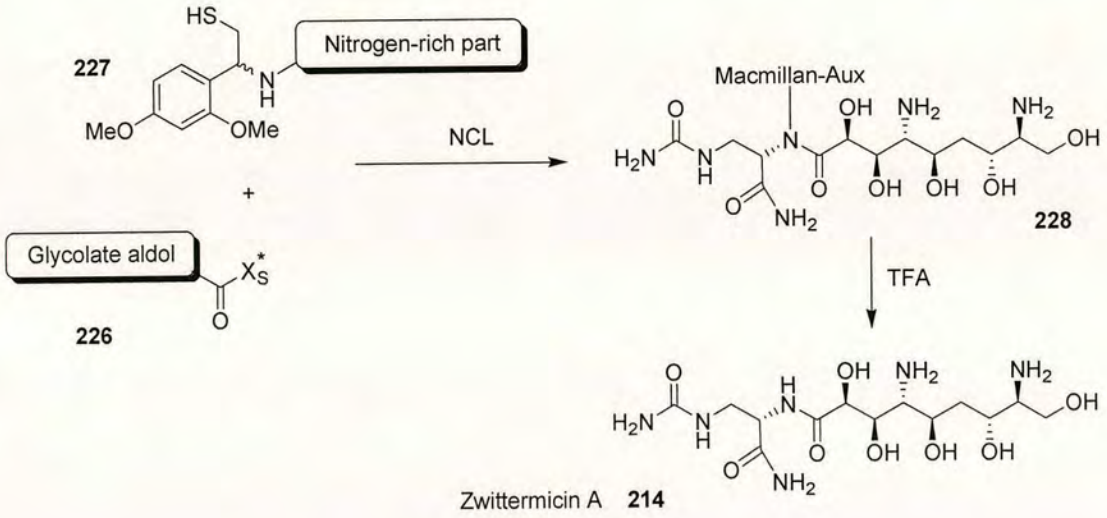
Scheme 78: Principle of Native Chemical Ligation.

The NCL of unprotected peptide segments has been demonstrated to be uniquely effective for the rapid and efficient synthesis of numerous proteins. However, the necessity of an N-terminal Cys residue at the ligation site is not always compatible with the synthetic target, limiting the use of the NCL in synthesis. For this reason, numerous examples of auxiliary-assisted peptide ligation have been investigated.[170-177] The development of these cleavable thiol auxiliaries enlarges the applicability of NCL to non-Cys targets. For example, the TFA-removable Macmillan auxiliary has been successfully used for Cys-free NCL (**scheme 79**).[177]



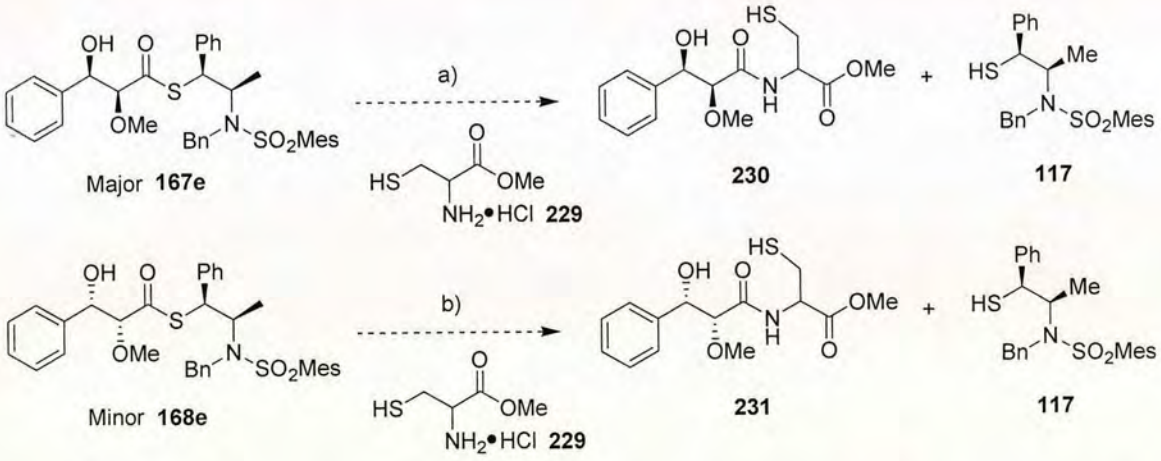
Scheme 79: Use of Macmillan's auxiliary in peptide synthesis.[177]

Thus, the NCL methodology could be used in the synthesis of zwittermicin A, leading to peptide bond formation between the unprotected glycolate aldol fragment **226** and the unprotected nitrogen-rich part attached to the Macmillan auxiliary **227** (**scheme 80**).



Scheme 80: Use of NCL in the synthesis of zwittermicin A.

Initial studies were undertaken to optimise the conditions of the original NCL in the reaction between a simple glycolate aldol-adduct and Cys methyl ester. The first attempt was carried out between glycolate aldol **167e** and Cys methyl ester **229** in aqueous buffer at pH 7.5; in the presence of 4-mercaptophenyl acetic acid (MPAA) as a reducing reagent to prevent the thiol of the Cys from oxidation, and also to increase the reactivity by forming new thiolester intermediates through transthiolesterification (**scheme 81**). Unfortunately, this first attempt was unsuccessful and only starting materials were recovered after 4 days. In spite of all the efforts to conduct the reaction in an inert atmosphere (the reaction was carried out under argon and the buffer solution was degassed under vacuum and flushed with argon prior to use), and the careful selection of the reagents (MPAA was chosen as catalyst based on reports of its high efficiency[172] in the NCL) the reaction failed to work, maybe due to the low solubility of aldol-adduct **168e** in aqueous conditions. Thus, a second attempt was conducted in DMF (**scheme 81**). However, the expected NCL did not occur and again only starting materials were recovered.



Scheme 81: Attempted NCL between glycolate aldol adducts and Cys methyl ester. Reagents and conditions: a) **229** (2.0 eq.), MPAA (250 mM), 6 M guanidine•HCl, 0.1 M Na_2HPO_4 buffer, pH 7.5, RT. b) **229** (2.0 eq.), MPAA (250 mM), DMF, RT.

Although our initial NCL studies were not successful, further investigations could be undertaken to optimise the solubility conditions and investigate a range of thiol additives; this could allow the peptide bond formation to take place, and therefore the possibility of using the optimised NCL conditions in the synthesis of zwittermicin A.

5.1.2 Development of Alternative Thiol Auxiliaries

An extension of our studies would include the development of alternative thiol auxiliaries to be used in selective propionate and glycolate boron-mediated aldol reactions. In our studies, we have proved the high selectivity and easy cleavage of the new thiol auxiliary **117**. However, the longer length of its synthetic route (five or six steps) compared with the Abiko-Masamune auxiliary (2 steps), together with its failure to give *syn*-propionate aldols, could be a limitation for its use in synthesis. Therefore, the development of alternative highly selective auxiliaries for *syn* and *anti* propionate and glycolate aldol reactions, that could be prepared in fewer steps, would be of high interest. Different auxiliaries derived from norephedrine or ephedrine (R^1 = Me) have been investigated by Abiko[33] leading to the development of the Abiko-Masamune auxiliary **232**, and therefore similar studies could also be undertaken with its thiol derivative **117** (**figure 29**).

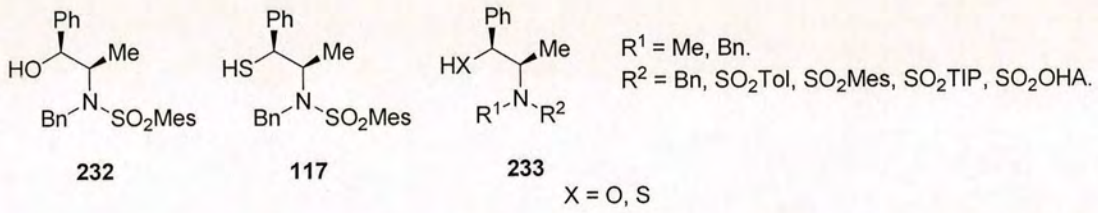


Figure 29: Abiko-Masamune auxiliary **232**, thiol auxiliary **117** and their possible alternatives (**233**, X = O, S).

CHAPTER 6: EXPERIMENTAL PROCEDURES

6.1 GENERAL EXPERIMENTAL

^{1}H nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock for the indicated reference at ambient probe temperatures on Varian Gemini 200 (200 MHz), Bruker AC250 (250MHz), Bruker DPX360 (360MHz) Fourier transform instruments. The data are presented as follows: chemical shift (in ppm on the δ scale relative to $\delta_{TMS} = 0$), integration, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant and the interpretation. ^{13}C NMR spectra were recorded using an internal deuterium lock for the indicated reference at ambient probe temperatures on Varian Gemini 200 (50.3 MHz), Bruker AC250 (62.9 MHz) or Bruker AM360 (90.6 MHz) instruments and are reported in ppm on the δ scale. Where Distortionless Enhancement Polarisation Transfer (DEPT) spectra have been reported, the carbon signals due to methyl (CH_3), methylene (CH_2), methine (CH) and quaternary carbon (C) are assigned.

Infra-red spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR instrument using 5 mm sodium chloride plates, or 0.1 mm sodium chloride solution cells. The wavelengths of maximum absorbance (ν_{max}) are quoted in cm^{-1}.

Electron impact (EI) and electrospray mass spectrometries were carried out on a Thermo MAT 900 XP mass spectrometer. Fast atom bombardment was performed on a Kratos MS50TC. The parent ion or fragment of highest mass is quoted, followed by significant fragments with relative intensities. Fast atom bombardment (FAB) mass spectra were performed on a Kratos MS50TC mass spectrometer. The parent ion or relevant fragments are quoted, followed by significant fragments and their relative intensities. Elemental analysis was carried out on a Perkin Elmer 2400 CHN Elemental analyser by the service at the University of St. Andrews.

Optical rotations were measured on an AA-1000 polarimeter with a path length of 1.0 dm at the sodium D line (589 nm) and are reported as follows: $[\alpha]_D$, concentration (c in g/100 ml), and solvent. All optical rotations were measured at room temperature.

Melting points were determined on a Gallenkamp Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck $60F_{254}$ (0.25 mm) glass silica plates and visualised by ultraviolet (UV) light and/or ammonium molybdate stain. Flash column chromatography was carried out on Merck Kieselgel 60 (Merck 9385) under positive pressure by means of an air line or hand pump. Eluent compositions are quoted as v/v ratios. High performance liquid chromatography (HPLC) was carried out on a Gilson instrument using a Spherisorb column (internal diameter: 20 mm) and equipped with a Gilson refractive index detector. All solvents to be used for HPLC analysis were vacuum filtered and degassed prior to use. All HPLC samples were filtered through 0.45 μm nylon syringe filters prior to analysis.

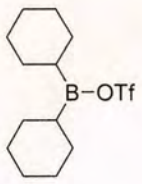
Reagents were purified by standard means. Dichloromethane (CH_2Cl_2), toluene, hexane, triethylamine (Et_3N), diisopropylethylamine (DIPEA), pyridine and 2,6-lutidine were distilled from calcium hydride and stored over calcium hydride under a nitrogen atmosphere. The aldehydes acrolein, methacrolein, isobutyraldehyde and isovaleraldehyde were freshly distilled from calcium chloride immediately prior to use. Benzaldehyde was distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl and stored under nitrogen atmosphere. All other reagents were used as supplied except where otherwise stated in the experimental text. Saturated aqueous solutions of inorganic salts are represented as: (volume, sat.).

All experiments were performed in an inert atmosphere of nitrogen or argon under anhydrous conditions using oven dried apparatus cooled in a desiccator or flame dried under nitrogen prior to use. Standard techniques for the handling of air-sensitive materials were employed.

INDEX OF GENERAL PROCEDURES

6.2 EXPERIMENTAL PROCEDURES FOR CHAPTER 2

Synthesis of Dicyclohexylboron Trifluoromethanesulfonate

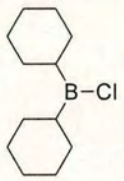


An oven-dried, 100 ml, round-bottomed flask capped with septum was charged with freshly distilled cyclohexene (7.0 ml, 0.07 mmol) and dry Et_2O (20 ml), and kept at 0 °C under nitrogen. Borane-dimethyl sulfide complex (3.2 ml, 0.03 mmol) was added dropwise over 10 min with stirring. The reaction mixture was stirred for 3 h at 0 °C and then the solid was allowed to settle without stirring. The supernatant organic solution was removed as much as possible by syringe, and the residual solid was dried under reduced pressure (vacuum line) to give dicyclohexylborane as a colourless solid.

The solid was suspended in dry hexane (20 ml) and trifluoromethanesulfonic acid (5.0 g, 0.03 mmol) was added dropwise via syringe over 20 min with constant stirring, during which time vigorous gas evolution occurred and the solid gradually dissolved. Stirring was continued at RT for 1 h and then the reaction mixture was left for 2 h without stirring. A semi-solid phase separated and the upper liquid was transferred via syringe into a dry, 100 ml, round-bottomed storage flask.

The solution was cooled to – 20 °C overnight, the hexane layer removed from the crystalline triflate and a stock solution 1.0 M of dicyclohexylboron trifluoromethanesulfonate in hexane was prepared.

Synthesis of Dicyclohexylboron Chloride



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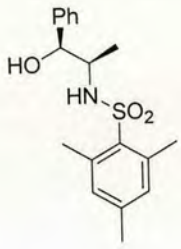
To a cooled (20 °C, water bath) stirred solution of freshly distilled cyclohexene (10.6 ml, 105 mmol) in dry Et_2O (20 ml) was added monochloroborane-methyl sulfide complex (5.2 ml, 50 mmol) dropwise. The reaction mixture was stirred for 2 h at 20 °C, and then the solvent was removed under reduced pressure (vacuum line), to give the chloroborane-methyl sulfide complex as a white solid. Distillation under reduced pressure gave dicyclohexylboron chloride as a colourless oil. The chloroborane could be stored in the freezer (- 20 °C) for several weeks without significant loss in activity. (Bp 98-104 °C, 1.0 mmHg).

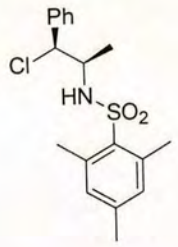
(1*S*,2*R*)-2-(*N*-Mesitylenesulfonylamino)-1-phenylpropan-1-ol 119[33]



To a stirred solution of (1*S*, 2*R*)-(+)-norephedrine (21.0 g, 139 mmol) and Et_3N (20.0 ml, 143 mmol) in dry CH_2Cl_2 (300 ml) was added mesitylenesulfonyl chloride (31.0 g, 142 mmol) at 0 °C. The reaction was stirred at 0 °C for 2 h. The reaction mixture was diluted with Et_2O (400 ml) and was washed with H_2O (2 × 200 ml), HCl (2 × 200 ml, 1 N aq), H_2O (2 × 200 ml), $NaHCO_3$ (2 × 200 ml, sat aq) and NaCl (2 × 200 ml, sat aq). The organics were dried ($MgSO_4$) and the volatiles removed under reduced pressure to give the sulfonamide **119** as a colourless solid which was recrystallised from CH_2Cl_2/hexane (44.0 g, 95%); $\mathbf{R_f}$ (25% EtOAc in hexane) = 0.24; **mp** 120-121 °C (CH_2Cl_2/hexane), lit.[33] 120.5-121.5 °C; $[\alpha]_D$ = 12.7 (c 1.10, $CHCl_3$), lit.[33] 12.8 (c 2.12, $CHCl_3$); ν_{max} (nujol)/cm^{-1} 3500 (OH), 3295 (NH), 1377 (SO_2N), 1155 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.30-7.12 (5H, m, Ar*H*), 6.90 (2H, s, Ar*H*), 4.90 (1H, br d, *J* = 9.1 Hz, C*H*Ph), 4.70 (1H, d, *J* = 3.2 Hz, N*H*), 3.45 (1H, dqd, *J* = 9.1, 6.8 & 3.2 Hz, C*H*CH_3), 2.60 (6H, s, *o*-CH_3), 2.24 (3H, s, *p*-CH_3), 0.80 (3H, d, *J* = 6.8 Hz, CH_3CH); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 141.66 (C), 139.66 (C), 138.26 (2 × C), 133.68 (C), 131.40 (2 × CH), 127.72 (2 × CH), 127.05 (CH), 125.37 (2 × CH), 75.01 (CH), 53.94 (CH), 22.35 (2 × CH_3), 20.30 (CH_3), 14.02 (CH_3); ***m/z*** (FAB, THIOG) 334 ($[M+H]^+$, 56 %), 316 (87), 183 (64), 134 (75), 119 (100), 91 (80), 77 (67); **HRMS** (FAB, THIOG) $[M+H]^+$ found 334.1472, $C_{18}H_{24}NO_3S$ requires 334.1476. Found: C, 64.4; H, 7.18; N, 4.04. $C_{18}H_{23}NO_3S$ requires: C, 64.8; H, 6.95; N, 4.20.

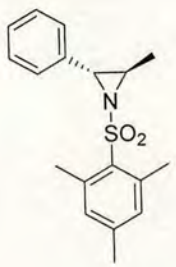
^{1}H spectroscopic data in good agreement with the literature.[33]

(1*S*,2*R*)-1-Chloro-2-(*N*-mesitylenesulfonylamino)-1-phenylpropane 120



To sulfonamide **119** (42.0 g, 126 mmol) was added thionyl chloride (30.0 ml, 411 mmol) and the reaction was stirred at RT for 15 h. The excess thionyl chloride was removed under reduced pressure to give the crude chloride as a brown oil. Trituration using Et_2O/hexane gave chloropropane **120** as a colourless solid (42.1 g, 95%); $\mathbf{R_f}$ (20% EtOAc in hexane) = 0.44; **mp** 137-138 °C; $[\alpha]_D$ = 27.2 (c 1.10, $CHCl_3$); ν_{max} (nujol)/cm^{-1} 3295 (NH), 1377 (SO_2N), 1151 (SO_2N), 723 (CCl); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.43-7.27 (5H, m, Ar*H*), 7.04 (2H, s, Ar*H*), 5.05 (1H, d, *J* = 3.2 Hz, N*H*), 4.96 (1H, br d, *J* = 9.5 Hz, C*H*Ph), 3.77 (1H, dqd, *J* = 9.5, 6.6 & 3.2 Hz, C*H*CH_3), 2.74 (6H, s, 2 × *o*-CH_3), 2.37 (3H, s, *p*-CH_3), 1.14 (3H, d, *J* = 6.6 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 142.29 (C), 138.78 (2 × C), 137.38 (C), 134.31 (C), 131.96 (2 × CH), 128.37 (2 × CH), 128.18 (CH), 126.97 (2 × CH), 67.89 (CH), 54.94 (CH), 22.86 (2 × CH_3), 20.81 (CH_3), 15.01 (CH_3); ***m/z*** (FAB, THIOG) 352 ([M+H]$^+$, 80%), 316 (73), 183 (68), 119 (100), 91 (84), 77 (71); **HRMS** (FAB, THIOG) [M+H]$^+$ found 352.1136, $C_{18}H_{23}ClNO_2S$ requires 352.1138. Found: C, 61.2; H, 6.30; N, 3.73. $C_{18}H_{22}ClNO_2S$ requires: C, 61.4; H, 6.30; N, 3.98.

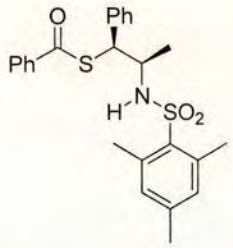
(2*R*,3*R*)-1-Mesitylenesulfonyl-2-methyl-3-phenylaziridine 121



Method A: To a solution of chloride **120** (35.0 g, 100 mmol) in DMF (150 ml) was added potassium *tert*-butoxide (13.5 g, 120 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and the reaction was stirred for a further 18 h at RT. NaCl (300 ml, sat aq) was added and the mixture was extracted with Et_2O (3 × 200 ml). The organics were combined and dried ($MgSO_4$) and volatiles were removed under reduced pressure to give a solid residue which was recrystallised from hexane to give the aziridine **121** as a colourless solid (29.0 g, 92%).

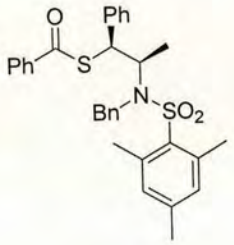
Method B: To (1*S*,2*R*)-2-(*N*-mesitylenesulfonylamino)-1-phenylpropan-1-ol **119** (2.0 g, 6.0 mmol) was added Et_3N (20 ml) at 0 °C. Methanesulfonyl chloride (1.0 ml, 13 mmol) was added dropwise with vigorous stirring. A pale yellow precipitate resulted upon addition. The reaction mixture was stirred at 0 °C for 10 min and then at RT for 14 h. NaCl (20 ml, sat aq) was added and the mixture was extracted with EtOAc (3 × 20 ml) and washed with NaCl (3 × 20 ml, sat aq). The organics were combined and dried ($MgSO_4$) and the volatiles removed under reduced pressure to give the aziridine **121** as a colourless solid which was recrystallised from hexane (1.60 g, 85%); $\mathbf{R_f}$ (20% EtOAc in hexane) = 0.65; **mp** 77-78 °C (hexane); $[\alpha]_D$ = – 31.8 (c 1.10, $CHCl_3$), ν_{max} (nujol) / cm^{-1} 1234 (SO_2N); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.58-7.46 (3H, m, Ar*H*), 7.45-7.35 (2H, m, Ar*H*), 7.17 (2H, s, Ar*H*), 4.07 (1H, d, *J* = 4.2 Hz, C*H*Ph), 3.13 (1H, qd, *J* = 5.9 & 4.2 Hz, C*H*CH_3), 2.97 (6H, s, *o*-CH_3), 2.52 (3H, s, *p*-CH_3), 2.10 (3H, d, *J* = 5.9 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 142.40 (C), 139.31 (2 × C), 136.03 (C), 134.92 (C), 131.58 (2 × CH), 128.36 (2 × CH), 127.80 (CH), 126.07 (2 × CH), 48.82 (CH), 48.63 (CH), 22.86 (2 × CH_3), 20.82 (CH_3), 14.21 (CH_3); ***m/z*** (FAB, THIOG) 316 ($[M+H]^+$, 93%), 314 (13), 183 (22), 167 (10), 165 (7); **HRMS** (FAB, THIOG) $[M+H]^+$ found 316.1372, $C_{18}H_{22}NO_2S$ requires 316.1371. Found: C, 68.4; H, 6.62; N, 4.17. $C_{18}H_{21}NO_2S$ requires: C, 68.5; H, 6.71; N, 4.44.

(1*S*,2*R*)-2-(*N*-Mesitylenesulfonylamino)-1-phenylpropyl thiolbenzoate 122



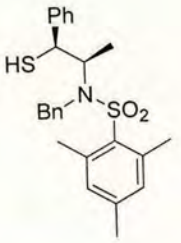
To a stirred solution of aziridine **121** (25.0 g, 79.4 mmol) and thiolbenzoic acid (11.6 g, 84.0 mmol) in MeCN (60 ml) was added tributylphosphine (2.10 ml, 8.40 mmol) followed by H_2O (50 ml) under nitrogen, and the resulting mixture was stirred at RT for 18 h. The mixture was extracted with CH_2Cl_2 (3 × 50 ml), washed with NaCl (2 × 50 ml, sat aq) and dried ($MgSO_4$). The organics were removed under reduced pressure to give the crude thiolbenzoate. Purification by flash chromatography (20% EtOAc in hexane) gave the thiolbenzoate ester **122** as a colourless solid (32.7 g, 91%); $\mathbf{R_f}$ (20% EtOAc in hexane) = 0.42; **mp** 101-102 °C; $[\alpha]_D$ 113 (c 1.10, $CHCl_3$); ν_{max} (nujol) / cm^{-1} 3288 (NH), 1659 (C=O), 1234 (SO_2N), 1159 (SO_2N); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.94 (2H, d, *J* = 7.2 Hz, Ar*H*), 7.70 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.55 (2H, t, *J* = 6.5 Hz, Ar*H*), 7.48-7.35 (5H, m , Ar*H*), 6.97 (2H, s, Ar*H*), 4.87 (1H, d, *J* = 4.2 Hz, N*H*), 4.75 (1H, d. *J* = 9.6 Hz, C*H*Ph), 3.97 (1H, dqd, *J* = 9.6, 6.6 & 4.2 Hz, C*H*CH_3), 2.76 (6H, s, 2 × *o*-C*H*$_3$), 2.29 (3H, s, *p*-C*H*$_3$), 1.37 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 189.75 (C), 143.04 (C), 139.01 (2 × C), 136.92 (C), 136.25 (C), 133.73 (C), 133.41 (CH), 131.78 (2 × CH), 128.53 (4 × CH), 128.37 (2 × CH), 127.84 (CH), 127.11 (2 × CH), 53.36 (2 × CH), 22.96 (2 × CH_3), 20.72 (CH_3), 20.08 (CH_3); ***m/z*** (FAB, THIOG) 455 ($[M+H]^+$, 47%), 316 (29), 255 (38), 226 (31), 183 (29); **HRMS** (FAB, THIOG) $[M+H]^+$ found 455.1511, $C_{25}H_{28}NO_3S_2$ requires 455.1511.

(1*S*,2*R*)-2-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1-phenylpropyl thiolbenzoate 123



To a solution of thiolbenzoate ester **122** (20.0 g, 44.1 mmol) in DMF (250 ml) was added NaH (1.97 g, 60% dispersion in mineral oil, 49.2 mmol) at 0 °C. The reaction was stirred for 30 min, benzyl bromide was added (5.66 ml, 47.6 mmol) and the reaction was stirred for a further 18 h at RT. NaCl (200 ml, sat aq) was added and the mixture was extracted with Et_2O (2 × 200 ml). The organics were combined and dried ($MgSO_4$) and volatiles were removed under reduced pressure to give the crude thiobenzoate. Recrystallisation from hexanes gave benzyl protected sulfonamide **123** as a colourless solid (23.7 g, 99%); $\mathbf{R_f}$ (20% EtOAc in hexane) = 0.47; **mp** 60-61 °C; $[\alpha]_D$ 71.3 (c 1.15, $CHCl_3$); ν_{max} (nujol) / cm^{-1} 1665 (C=O), 1234 (SO_2N), 1155 (SO_2N); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 8.07 (2H, d, *J* = 7.1 Hz, Ar*H*), 7.80 – 7.30 (9H, m, Ar*H*), 7.25 (2H, t, *J* = 8.5 Hz, Ar*H*), 7.05 (2H, s, Ar*H*), 7.01 (2H, d, *J* = 7.0 Hz, Ar*H*), 5.26 (1H, d, *J* = 9.0 Hz, C*H*Ph), 5.07 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.75 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.50 (1H, qn, *J* = 9.0 & 6.8 Hz, $CHCH_3$), 2.55 (6H, s, 2 × *o*-CH_3), 2.51 (3H, s, *p*-CH_3), 1.57 (3H, d, *J* = 6.8 Hz, $CHCH_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 189.58 (C), 142.78 (C), 141.03 (2 × C), 140.54 (C), 138.96 (C), 136.88 (C), 134.00 (CH), 133.31 (C), 132.59 (2 × CH), 129.17 (2 × CH), 129.02 (2 × CH), 128.87 (2 × CH), 128.83 (2 × CH), 128.14 (2 × CH), 127.83 (2 × CH), 127.75 (CH), 127.66 (CH), 57.18 (CH), 51.93 (CH), 47.93 (CH_2), 23.34 (2 × CH_3), 21.35 (CH_3), 17.97 (CH_3); ***m/z*** (FAB, NOBA) 544 ($[M+H]^+$, 11%), 406 (16), 362 (10), 317 (20), 316 (51); **HRMS** (FAB, NOBA) $[M+H]^+$ found 544.1980, $C_{32}H_{34}NO_3S_2$ requires 544.1980.

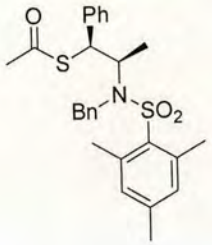
(1*S*,2*R*)-2-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1-phenylpropan-1-thiol 117



Method A: To a solution of thiolbenzoate ester **123** (15.0 g, 27.6 mmol) in THF (100 ml) at 0 °C was added $LiAlH_4$ (1.20 g, 31.6 mmol). The reaction mixture was warmed to RT and stirred for 2.5 h. The reaction mixture was cooled to 0 °C, $Na_2SO_4 \bullet 10H_2O$ was added slowly and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through celite and the organics removed under reduced pressure to give the crude thiol as an oil. Purification by flash chromatography (20% EtOAc in hexane) gave thiol **117** as a colourless solid (11.3 g, 93%).

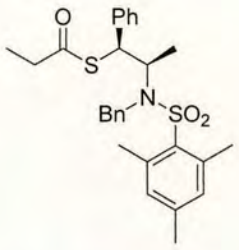
Method B: To a stirred suspension of thiolbenzoate ester **123** (1.8 g, 3.3 mmol) in MeOH (20 ml) was added NaOMe (5.1 ml, 1 M in MeOH, 5.1 mmol) at RT. The reaction mixture was stirred at RT for 1.5 h. Cation exchange resin AG 50W-X8 in its hydrogen form was added and the mixture stirred for 20 min until a neutral pH was reached. The reaction mixture was filtered to recover the resin and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) gave thiol **117** as a colourless solid (1.39 g, 96%); $\mathbf{R_f}$ (10% EtOAc in hexane) = 0.41; $\mathbf{R_f}$ (20% EtOAc in hexane) = 0.60; **mp** 57-58 °C; $[\alpha]_D$ -10.9 (c 1.10, $CHCl_3$); ν_{max} (nujol) / cm^{-1} 2558 (SH), 1376 (SO_2N), 1152 (SO_2N); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.60-7.25 (8H, m, Ar*H*), 7.10 – 7.00 (4H, m, Ar*H*), 4.95 (1H, d, J = 16.2 Hz, CH_AH$_B$Ph), 4.70 (1H, d, J = 16.2 Hz, CH$_A$$H_B$Ph), 4.45 – 4.30 (2H, m, C*H*CH$_3$ & C*H*Ph), 2.57 (6H, s, 2 × *o*-CH_3), 2.51 (3H, s, *p*-CH_3), 1.97 (1H, d, J = 4.2 Hz, S*H*), 1.53 (3H, d, J = 6.6 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 142.80 (C), 142.58 (C), 140.93 (2 × C), 138.93 (C), 133.40 (C), 132.56 (2 × CH), 128.93 (2 × CH), 128.85 (2 × CH), 128.77 (2 × CH), 127.84 (CH), 127.62 (CH), 127.48 (2 × CH), 58.58 (CH), 48.83 (CH), 48.28 (CH_2), 23.34 (2 × CH_3), 21.33 (CH_3), 17.51 (CH_3); ***m/z*** (FAB, THIOG) 440 ($[M+H]^+$, 15%), 406 (13), 317 (30), 316 (81), 91 (100); **HRMS** (FAB, THIOG) $[M+H]^+$ found 440.1725, $C_{25}H_{30}NO_2S_2$ requires 440.1718.

(1*S*,2*R*)-2-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1-phenylpropyl thiolacetate 128



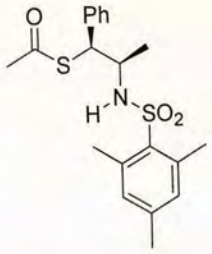
To a solution of thiol **117** (200 mg, 0.456 mmol) in CH_2Cl_2 (10 ml) was added pyridine (89 µl, 1.1 mmol) followed by acetyl chloride (80 µl, 0.91 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 18 h. The reaction mixture was diluted with Et_2O (20 ml) and was washed with H_2O (20 ml), HCl (20 ml, 1 N aq), H_2O (20 ml), $NaHCO_3$ (20 ml, sat aq) and NaCl (20 ml, sat aq). The organics were dried ($MgSO_4$) and volatiles were removed under reduced pressure to give the crude thiolester as a colourless oil. Purification by flash chromatography (10% EtOAc in hexane) gave the thiolacetate ester **128** as a colourless oil (199 mg, 91%); $\mathbf{R_f}$ 10% EtOAc in hexane) = 0.25; $\mathbf{[\alpha]_D}$ 65.7 (c 8.05, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1696 (C=O), 1603 (Ar), 1495 (Ar), 1154 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.64 (2H, d, J = 7.6 Hz, Ar*H*), 7.49 – 7.43 (3H, m, Ar*H*), 7.33 (1H, d, J = 7.3 Hz, Ar*H*), 7.22 (2H, t, J = 6.3 Hz, Ar*H*), 7.01 (2H, s, Ar*H*), 6.88 (2H, d, J = 7.1 Hz, Ar*H*), 4.98 (1H, d, J = 16.2 Hz, CH_AH_BPh), 4.97 (1H, d, J = 9.3 Hz, C*H*Ph), 4.65 (1H, d, J = 16.2 Hz, CH_AH_BPh), 4.36 (1H, dq, J = 9.3 & 6.8 Hz, C*H*CH_3), 2.49 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 2.39 (3H, s, CH_3CO), 1.46 (3H, d, J = 6.8 Hz, CHCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 193.37 (C), 142.74 (C), 140.99 (2 × C), 140.46 (C), 138.91 (C), 133.22 (C), 132.56 (2 × CH), 129.19 (2 × CH), 128.87 (2 × CH), 128.80 (2 × CH), 127.96 (2 × CH), 127.85 (CH), 127.64 (CH), 56.87 (CH), 52.00 (CH), 47.81 (CH_2), 30.76 (CH_3), 23.29 (2 × CH_3), 21.32 (CH_3), 17.91 (CH_3); ***m/z*** (FAB, THIOG) 482 ($[M+H]^+$, 16%), 316 (30), 183 (15), 119 (73), 91 (100), 77 (48), 75 (10), 43 (74); **HRMS** (FAB, THIOG) $[M+H]^+$ found 482.1828, $C_{27}H_{32}NO_3S_2$ requires 482.1824.

(1*S*,2*R*)-2-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1-phenylpropyl thiolpropionate 131



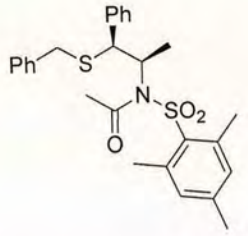
To a solution of thiol **117** (9.00 g, 20.5 mmol) in CH_2Cl_2 (100 ml) was added pyridine (2.18 ml, 27.0 mmol) followed by propionyl chloride (2.19 ml, 36.0 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 18 h. The reaction mixture was diluted with Et_2O (300 ml) and was washed with H_2O (200 ml), HCl (200 ml, 1 N aq), H_2O (200 ml), $NaHCO_3$ (200 ml, sat aq) and NaCl (200 ml, sat aq). The organics were dried ($MgSO_4$) and volatiles were removed under reduced pressure to give the crude thiolester as a colourless oil. Purification by flash chromatography (20% EtOAc in hexane) gave the thiolpropionate ester **131** as a colourless solid (9.39 g, 93%); $\mathbf{R_f}$ (20% EtOAc in hexane) = 0.56; **mp** 60-61 °C; $[\alpha]_D$ 71.3 (c 1.15, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1697 (C=O), 1375 (SO_2N), 1147 (SO_2N); **^{1}H NMR** δ (360 MHz, $CDCl_3$) 7.30 (2H, d, *J* = 7.6 Hz, Ar*H*), 7.20 – 7.06 (3H, m, Ar*H*), 7.00 (1H, t, *J* = 7.4 Hz, Ar*H*), 6.87 (2H, t, *J* = 6.3 Hz, Ar*H*), 6.69 (2H, s, Ar*H*), 6.55 (2H, d, *J* = 7.0 Hz, Ar*H*), 4.65 (1H, d, *J* = 16.2 Hz, CH_AH$_B$Ph), 4.64 (1H, d, *J* = 9.2 Hz, C*H*Ph), 4.31 (1H, d, *J* = 16.2 Hz, CH$_A$$H_B$Ph), 4.01 (1H, dq, *J* = 9.2 & 6.8 Hz, C*H*CH$_3$), 2.32 (2H, q, *J* = 7.5 Hz, CH_2CH$_3$), 2.16 (3H, s, *p*-CH_3), 2.15 (6H, s, 2 × *o*-CH_3), 1.14 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.95 (3H, t, *J* = 7.5 Hz, CH$_2$CH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 197.83 (C), 142.72 (C), 141.00 (2 × C), 140.56 (C), 138.93 (C), 133.21 (C), 132.54 (2 × CH), 129.15 (2 × CH), 128.85 (4 × CH), 127.94 (2 × CH), 127.81 (CH), 127.58 (CH), 56.96 (CH), 51.51 (CH), 47.79 (CH_2), 37.63 (CH_2), 23.29 (2 × CH_3), 21.32 (CH_3), 17.86 (CH_3), 9.82 (CH_3); ***m/z*** (FAB, THIOG) 496 ($[M+H]^+$, 8%), 406 (24), 316 (54), 207 (53), 91 (100); **HRMS** (FAB, NOBA) $[M+H]^+$ found 496.1985, $C_{28}H_{34}NO_3S_2$ requires 496.1980. Found: C, 67.9; H, 6.17; N, 2.65. $C_{28}H_{33}NO_3S_2$ requires: C, 67.8; H, 6.71; N, 2.83.

(1*S*,2*R*)-2-(*N*-Mesitylenesulfonylamino)-1-phenylpropyl thiolacetate 132



To a stirred solution of aziridine **121** (2.0 g, 6.3 mmol) and thiolacetic acid (0.52 ml, 6.9 mmol) in MeCN (15 ml) was added tributylphosphine (0.16 ml, 0.63 mmol) followed by H_2O (10 ml) under nitrogen, and the resulting mixture was stirred at RT for 18 h. The mixture was extracted with EtOAc (3 × 30 ml), washed with NaCl (2 × 30 ml, sat aq) and dried ($MgSO_4$). The organics were removed under reduced pressure to give the crude thiolacetate. Purification by flash chromatography (20% EtOAc in hexane) gave the thiolacetate ester **132** as a colourless oil (1.7 g, 68%); $\mathbf{R_f}$ (20% EtOAc in hexane) = 0.38; $[\alpha]_D$ 195 (c 1.0, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3270 (NH), 1693 (C=O), 1603 (Ar), 1493 (Ar), 1155 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.21-7.11 (3H, m, Ar*H*), 7.10-7.02 (2H, m, Ar*H*), 6.85 (2H, s, Ar*H*), 4.72 (1H, d, *J* = 9.4 Hz, C*H*Ph), 4.46 (1H, d, *J* = 4.9 Hz, N*H*), 3.60 (1H, dqd, *J* = 9.4, 6.6 & 4.9 Hz, C*H*CH_3), 2.51 (6H, s, *o*-CH_3), 2.21 (3H, s, *p*-CH_3), 2.19 (3H, s, CH_3CO), 1.07 (3H, d, *J* = 6.6 Hz, CH_3CH); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 194.30 (C), 142.49 (C), 139.56 (2 × C), 137.77 (C), 134.44 (C), 132.31 (2 × CH), 128.98 (2 × CH), 128.80 (2 × CH), 128.19 (CH), 53.93 (CH), 53.70 (CH), 30.74 (CH_3), 23.41 (2 × CH_3), 21.28 (CH_3), 20.11 (CH_3); ***m/z*** (FAB, THIOG) 392 ($[M+H]^+$, 39%), 316 (33), 183 (48), 119 (100), 77 (35), 43 (81); **HRMS** (FAB, 3-NOBA) $[M+H]^+$ found 392.1352, $C_{20}H_{26}NO_3S_2$ requires 392.1354.

(1*S*,2*R*)-2-(*N*-Acetamido-*N*-mesitylenesulfonylamino)-(S-benzyl)-1-phenyl-propan-1-thiol 133



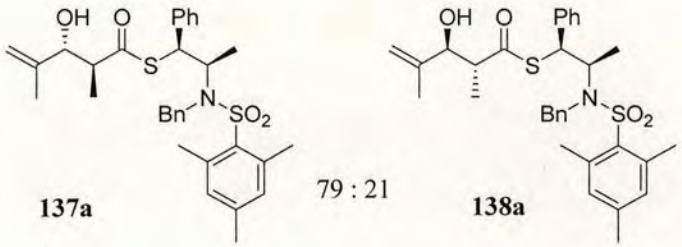
To a solution of thiolacetate ester **132** (1.36 g, 3.48 mmol) in DMF (20 ml) was added NaH (153 mg, 60% dispersion in mineral oil, 3.83 mmol) at 0 °C. The reaction was stirred for 30 min, benzyl bromide was added (0.46 ml, 3.8 mmol) and the reaction was stirred for a further 18 h at RT. NaCl (30 ml, sat aq) was added and the mixture was extracted with Et_2O (3 × 30 ml). The organics were combined and dried ($MgSO_4$) and volatiles were removed under reduced pressure to give a crude oil. Purification by flash chromatography (10% EtOAc in hexane) gave **133** as a colourless oil (1.57 g, 94%); $\mathbf{R_f}$ (10% EtOAc in hexane) = 0.33; $[\alpha]_D$ 5.6 (c 2.3, $CHCl_3$); ν_{max} (neat) / cm^{-1} 1691 (C=O), 1602 (Ar), 1493 (Ar); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.25-7.06 (10H, m, Ar*H*), 7.05 (2H, s, Ar*H*), 4.47 (1H, d, *J* = 10.2 Hz, C*H*Ph), 3.75 (1H, dq, *J* = 10.2 & 6.6 Hz, C*H*CH_3), 3.43 (1H, d, *J* = 13.0 Hz, C$H_A$$H_B$Ph), 3.35 (1H, d, *J* = 13.0 Hz, C$H_A$$H_B$Ph), 2.43 (6H, s, *o*-C$H_3$), 2.35 (3H, s, C$H_3$CO), 2.19 (3H, s, *p*-C$H_3$), 1.41 (3H, d, *J* = 6.6 Hz, CH_3CH); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 172.13 (C), 144.39 (C), 140.47 (2 × C), 139.51 (C), 137.99 (C), 132.97 (2 × CH), 132.54 (C), 129.70 (2 × CH), 129.49 (2 × CH), 129.30 (2 × CH), 128.55 (2 × CH), 127.95 (CH), 127.44 (CH), 59.91 (CH), 53.68 (CH), 36.71 (CH_2), 28.33 (CH_3), 23.13 (2 × CH_3), 21.34 (CH_3), 17.64 (CH_3); ***m/z*** (FAB, THIOG) 482 ($[M+H]^+$, 6%), 119 (90), 91 (100), 79 (70), 77 (67), 43 (85); **HRMS** (FAB, 3-NOBA) $[M+H]^+$ found 482.1823, $C_{27}H_{32}NO_3S_2$ requires 482.1824.

General procedure A: Synthesis of *Anti* Propionate Aldol Adducts

To a stirred solution of thiolpropionate ester **131** (200 mg, 0.404 mmol) in solvent (20 ml) at – 78 °C was added boron triflate or chloride (0.81 mmol) then amine base (1.2 mmol). The reaction mixture was stirred at – 78 °C for 2 h, then aldehyde was added (1.2 mmol). The reaction was stirred at – 78 °C for 1.5 h and warmed to 0 °C for 1 h. The mixture was quenched by the addition of pH 7 buffer and methanol (1:1, 4 ml) and diluted with methanol (6 ml) to make a homogeneous solution. After careful addition of H_2O_2 (30% aq, 2 ml) the mixture was stirred at RT for 1 h.

NaCl (30 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 ml). The combined organics were washed with $NaHCO_3$ (30 ml, sat aq) and NaCl (30 ml, sat aq), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldol product. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers that was separated by **HPLC**.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-2,4-dimethyl-3-hydroxythiolpent-4-eneoate 137a



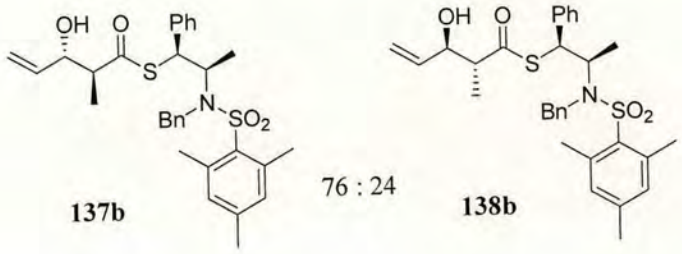
137a 79 : 21 **138a**

General procedure A was followed with thiolpropionate ester **131** (200 mg, 0.404 mmol), dibutylboron triflate (1.0 M in hexane, 0.81 ml, 0.81 mmol), diisopropylethylamine (0.21 ml, 1.2 mmol) and methacrolein (0.11 ml, 1.2 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137a** and **138a** that was separated by **HPLC** (199 mg, 87%) (ds $_{anti\,:\,anti}$ = 79 : 21, ds $_{anti\,:\,syn}$ = 99 : 1).

(2*S*,3*R*)-Major diastereoisomer 137a: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 71 min; **R_f** (20% EtOAc in hexane) = 0.35; **$[\alpha]_D$** = + 77 (c 5.0, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3512 (OH), 1683 (C=O), 1153 (SO_2N), 958 (CH_2CH); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.65 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.55 - 7.42 (3H, m, Ar*H*), 7.35 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.23 (2H, t, *J* = 7.7 Hz, Ar*H*), 7.03 (2H, s, Ar*H*), 6.85 (2H, d, *J* = 7.1 Hz, Ar*H*), 5.12 (1H, br s, CCH_3=C$H_C$$H_D$), 5.09 (1H, br s, CCH_3=$CH_C$$H_D$), 5.02 (1H, d, *J* = 8.9 Hz, C*H*Ph), 4.99 (1H, d, *J* = 16.3 Hz, C$H_A$$H_B$Ph), 4.68 (1H, d, *J* = 16.3 Hz, $CH_A$$H_B$Ph), 4.42 - 4.30 (2H, m, C*H*OH & C(2')*H*CH_3), 2.96 (1H, dq ≡ qn, *J* = 7.1, C*H*CH_3), 2.51 (6H, s, 2 × *o*-CH_3), 2.50 (3H, s, *p*-CH_3), 1.89 (3H, s, CCH_3=CH_2), 1.49 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.17 (3H, d, *J* = 7.1 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 200.99 (C), 144.49 (C), 142.70 (C), 140.97 (2 × C), 140.15 (C), 138.90 (C), 133.25 (C), 132.51 (2 × CH), 129.11 (2 × CH), 128.83 (2 × CH), 128.73 (2 × CH), 127.91 (2 × CH), 127.74 (CH), 127.60 (CH), 114.74 (CH_2), 78.73 (CH), 57.26 (CH), 51.77 (CH), 51.58 (CH), 47.69 (CH_2), 23.28 (2 × CH_3), 21.29 (CH_3), 17.58 (CH_3), 17.19 (CH_3), 15.24 (CH_3); ***m/z*** (FAB, THIOG) 566 ($[M+H]^+$, 99%), 492 (12), 406 (57), 384 (52), 316 (75), 183 (56), 91 (100); **HRMS** (FAB, THIOG) $[M+H]^+$ found 566.2410, $C_{32}H_{40}NO_4S_2$ requires 566.2399.

(2*R*,3*S*)-Minor diastereoisomer 138a: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 84 min; **R_f** (20% EtOAc in hexane) = 0.31; **$[\alpha]_D$** = + 21 (c 0.65, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3511 (OH), 1687 (C=O), 1153 (SO_2N), 958 (CH_2CH); **^1H NMR** δ (250 MHz, $CDCl_3$) 7.53, (2H, d, *J* = 7.6 Hz, Ar*H*), 7.43 - 7.30 (3H, m, Ar*H*), 7.23 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.11 (2H, t, *J* = 6.3 Hz, Ar*H*), 6.92 (2H, s, Ar*H*), 6.79 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.96 (1H, br s, $=CH_CH_D$), 4.93 (1H, br s, $=CH_CH_D$), 4.90 (1H, d, *J* = 9.0 Hz, C*H*Ph), 4.89 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.55 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.34 - 4.18 (2H, m, C*H*OH & C*H*CH_3), 2.83 (1H, dq ≡ qn, *J* = 7.1, C*H*CH_3), 2.40 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 2.22 (1H, d, *J* = 4.8 Hz, O*H*) 1.70 (3H, s, $CCH_3=CH_2$), 1.37 (3H, d, *J* = 6.8 Hz, $CHCH_3$), 1.14 (3H, d, *J* = 7.1 Hz, $CHCH_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 200.79 (C), 144.03 (C), 142.51 (C), 140.73 (2 × C), 139.80 (C), 138.62 (C), 133.01 (C), 132.30 (2 × CH), 128.80 (2 × CH), 128.56 (2 × CH), 128.54 (2 × CH), 127.78 (2 × CH), 127.55 (CH), 127.36 (CH), 114.55 (CH_2), 78.39 (CH), 56.84 (CH), 51.66 (CH), 51.49 (CH), 47.65 (CH_2), 23.05 (2 × CH_3), 21.06 (CH_3), 17.42 (CH_3), 16.85 (CH_3), 15.24 (CH_3); ***m/z*** (FAB, THIOG) 566 ($[M+H]^+$, 42%), 406 (45), 316 (60), 289 (14), 183 (44), 119 (69), 91 (87); **HRMS** (FAB, 3-NOBA) $[M+H]^+$ found 566.2396, $C_{32}H_{40}NO_4S_2$ requires 566.2399.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-hydroxy-2-methyl-thiolpent-4-eneoate 137b



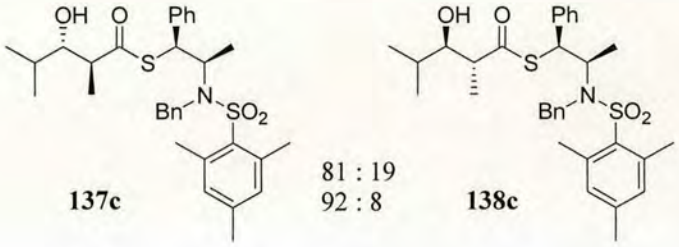
137b 76 : 24 **138b**

General procedure A was followed with thiolpropionate ester **131** (200 mg, 0.404 mmol), dibutylboron triflate (1.0 M in hexane, 0.81 ml, 0.81 mmol), diisopropylethylamine (0.21 ml, 1.2 mmol) and acrolein (0.11 ml, 1.2 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137b** and **138b** that was separated by **HPLC** (199 mg, 89%) (ds $_{anti}$: $_{anti}$ = 76 : 24, ds $_{anti : syn}$ = 99 : 1).

(2*S*,3*R*)-Major diastereoisomer 137b: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 66 min; R_f (20% EtOAc in hexane) = 0.32; $[\alpha]_D$ = + 72 (c 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3516 (OH), 1683 (C=O), 1603 (Ar), 1495 (Ar), 1153 (SO_2N), 952 (CH_2CH); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.58, (2H, d, *J* = 8.0 Hz, Ar*H*), 7.43 - 7.40 (3H, m, Ar*H*), 7.30 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.18 (2H, t, *J* = 7.7 Hz, Ar*H*), 6.97 (2H, s, Ar*H*), 6.81 (2H, d, *J* = 7.0 Hz, Ar*H*), 6.00-5.85 (1H, ddd, *J* = 17.0, 10.3 & 6.5 Hz, CH_2=C*H*), 5.40 (1H, dt, *J* = 17.0 & 1.3 Hz, =CH_CH$_D$), 5.32 (1H, dt, *J* = 10.3 & 1.3 Hz, =CH$_C$*H*$_D$), 4.96 (1H, d, *J* = 8.8 Hz, C*H*Ph), 4.92 (1H, d, *J* = 16.3 Hz, CH_AH$_B$Ph), 4.63 (1H, d, *J* = 16.3 Hz, CH$_A$*H*$_B$Ph), 4.39 - 4.23 (2H, m, C*H*OH & C(2')*H*CH_3), 2.80 (1H, dq ≡ qn, *J* = 7.1, C*H*CH_3), 2.45 (6H, s, 2 × *o*-C*H*$_3$), 2.44 (3H, s, *p*-C*H*$_3$), 1.42 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$) 1.20 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$); **^{13}C NMR** δ (90.5 MHz, CDCl3) 200.69 (C), 142.72 (C), 140.96 (2 × C), 140.13 (C), 138.85 (C), 138.17 (CH), 133.25 (C), 132.51 (2 × CH), 129.07 (2 × CH), 128.84 (2 × CH), 128.73 (2 × CH), 127.92 (2 × CH), 127.75 (CH), 127.63 (CH), 117.59 (CH_2), 75.58 (CH), 57.21 (CH), 54.03 (CH), 51.62 (CH), 47.73 (CH_2), 23.29 (2 × CH_3), 21.29 (CH_3), 17.61 (CH_3), 14.87 (CH_3); ***m/z*** (FAB, 3-NOBA) 552 ($[M+H]^+$, 96%), 406 (73), 316 (100), 289 (70), 183 (63), 145 (38), 119 (74), 113 (62), 91 (80); **HRMS** (FAB, THIOG) $[M+H]^+$ found 552.2242, $C_{31}H_{38}NO_4S_2$ requires 552.2242.

(2*R*,3*S*)-Minor diastereoisomer 138b: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 78 min; R_f (20% EtOAc in hexane) = 0.28; $[\alpha]_D$ = + 35 (c 1.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3511 (OH), 1685 (C=O), 1603 (Ar), 1495 (Ar), 1153 (SO_2N), 959 (CH_2CH); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.35, (2H, d, *J* = 8.0 Hz, Ar*H*), 7.25 - 7.15 (3H, m, Ar*H*), 7.07 (1H, t, *J* = 7.4 Hz, Ar*H*), 6.94 (2H, t, *J* = 8.1 Hz, Ar*H*), 6.75 (2H, s, Ar*H*), 6.62 (2H, d, *J* = 7.0 Hz, Ar*H*), 5.60 (1H, ddd, *J* = 17.0, 10.3 & 6.5 Hz, CH_2=C*H*), 5.10 (1H, dt, *J* = 17.0 & 1.3 Hz, CH=C$H_C$$H_D$), 5.02 (1H, dt, *J* = 10.3 & 1.3 Hz, CH=C$H_C$$H_D$), 4.74 (1H, d, *J* = 8.9 Hz, C*H*Ph), 4.72 (1H, d, *J* = 16.3 Hz, C$H_A$$H_B$Ph), 4.38 (1H, d, *J* = 16.3 Hz, C$H_A$$H_B$Ph), 4.17 - 4.00 (2H, m, C*H*OH & C(2')*H*CH_3), 2.59 (1H, dq ≡ qn, *J* = 7.1, C*H*CH_3), 2.23 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 1.20 (3H, d, *J* = 6.8 Hz, CHCH_3) 1.06 (3H, d, *J* = 7.1 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 200.18 (C), 142.25 (C), 140.44 (2 × C), 139.47 (C), 138.29 (C), 137.29 (CH), 132.60 (C), 132.01 (2 × CH), 128.50 (2 × CH), 128.34 (2 × CH), 128.29 (2 × CH), 127.44 (2 × CH), 127.41 (CH), 127.27 (CH), 117.05 (CH_2), 74.90 (CH), 56.49 (CH), 53.43 (CH), 51.13 (CH), 47.32 (CH_2), 22.77 (2 × CH_3), 20.80 (CH_3), 17.15 (CH_3), 14.45 (CH_3); ***m/z*** (FAB, 3-NOBA) 552 ($[M+H]^+$, 54%), 406 (49), 316 (85), 289 (53), 183 (53), 119 (82), 91 (90); **HRMS** (FAB, THIOG) $[M+H]^+$ found 552.2244, $C_{31}H_{38}NO_4S_2$ requires 552.2242.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-2,4-dimethyl-3-hydroxy-thiolpentanoate 137c



137c 81 : 19 92 : 8 **138c**

Method A: General procedure A was followed with thiolpropionate ester **131** (200 mg, 0.404 mmol), dibutylboron triflate (1.0 M in hexane, 0.81 ml, 0.81 mmol), diisopropylethylamine (0.21 ml, 1.2 mmol) and isobutyraldehyde (0.11 ml, 1.2 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137c** and **138c** that was separated by **HPLC** (215 mg, 94%) (ds $_{anti\,:\,anti}$ = 81 : 19, ds $_{anti\,:\,syn}$ = 99 : 1).

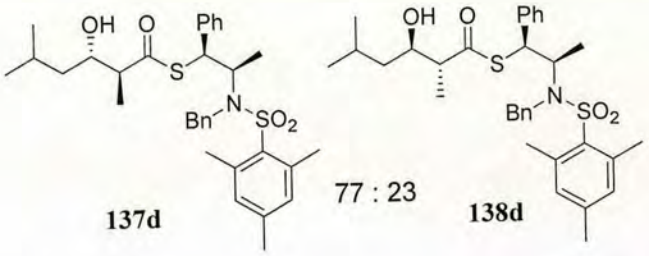
(2*S*,3*S*)-Major diastereoisomer 137c: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 63 min; **R_f** (20% EtOAc in hexane) = 0.37; **$[\alpha]_D$** = + 84 (c 4.2, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3532 (OH), 1681 (C=O), 1604 (Ar), 1495 (Ar), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.56 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.45-7.35 (3H, m, Ar*H*), 7.28 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.16 (2H, t, *J* = 7.8 Hz, Ar*H*), 6.96 (2H, s, Ar*H*), 6.81 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.94 (1H, d, *J* = 9.0 Hz, C*H*Ph), 4.92 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.61 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.32 (1H, dq, *J* = 9.0 & 6.8 Hz, C(2')*H*CH_3), 3.52 (1H, ddd = q, *J* = 6.9 Hz, C*H*OH), 2.90 (1H, dq ≡ qn, *J* = 6.9 Hz, C*H*CH_3), 2.44 (9H, s, 2 × *o*-C*H*$_3$ & *p*-C*H*$_3$), 2.26 (1H, d, *J* = 7.3 Hz, O*H*), 1.84-176 (1H, m, C*H*$(CH_3)_2$), 1.43 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 1.21 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 1.05 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3$)$_A$(CH_3)$_B$), 1.01 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 201.89 (C), 142.72 (C), 140.95 (2 × C), 140.12 (C), 138.81 (C), 133.21 (C), 132.51 (2 × CH), 129.09 (2 × CH), 128.84 (2 × CH), 128.74 (2 × CH), 127.90 (2 × CH), 127.78 (CH), 127.62 (CH), 78.95 (CH), 57.15 (CH), 51.72 (CH), 51.53 (CH), 47.75 (CH_2), 31.26 (CH), 23.28 (2 × CH_3), 21.29 (CH_3), 20.17 (CH_3), 17.66 (CH_3), 16.53 (CH_3), 15.61 (CH_3); ***m/z*** (FAB, THIOG) 568 ($[M+H]^+$, 99%), 406 (25), 386 (25), 316

(58), 183 (42), 119 (76), 91 (100); **HRMS** (FAB, 3-NOBA) $[M+H]^+$ found 568.2557, $C_{32}H_{42}NO_4S_2$ requires 568.2555.

(2*R*,3*R*)-Minor diastereoisomer 138c: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 72 min; R_f (20% EtOAc in hexane) = 0.28; $[\alpha]_D$ = + 38 (c 2.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3533 (OH), 1681 (C=O), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.54 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.45-7.36 (3H, m, Ar*H*), 7.27 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.15 (2H, t, *J* = 7.4 Hz, Ar*H*), 6.95 (2H, s, Ar*H*), 6.81 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.91 (1H, d, *J* = 8.9 Hz, C*H*Ph), 4.90 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.57 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.30 (1H, dq, *J* = 8.9 & 6.8 Hz, C(2')*H*CH_3), 3.48 (1H, br q, *J* = 5.1 Hz, C*H*OH), 2.86 (1H, dq ≡ qn, *J* = 7.1 Hz, C*H*CH_3), 2.43 (6H, s, 2 × *o*-CH_3), 2.42 (3H, s, *p*-CH_3), 2.20 (1H, br d, *J* = 6.6 Hz, O*H*), 1.71-1.63 (1H, m, C*H*$(CH_3)_2$), 1.39 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.30 (3H, d, *J* = 7.1 Hz, CHCH_3), 0.96 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_A(CH_3)_B$), 0.92 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_A(CH_3)_B$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 201.60 (C), 142.40 (C), 140.58 (2 × C), 139.66 (C), 138.45 (C), 132.80 (C), 132.16 (2 × CH), 128.63 (2 × CH), 128.44 (2 × CH), 128.41 (2 × CH), 127.59 (2 × CH), 127.42 (CH), 127.24 (CH), 78.64 (CH), 56.66 (CH), 51.25 (CH), 51.24 (CH), 47.50 (CH_2), 30.83 (CH), 22.92 (2 × CH_3), 20.94 (CH_3), 19.78 (CH_3), 17.27 (CH_3), 16.17 (CH_3), 15.56 (CH_3); ***m/z*** (FAB, 3-NOBA) 568 ($[M+H]^+$, 66%), 524 (22), 406 (46), 316 (89), 289 (68), 183 (62), 161 (13), 129 (68), 119 (92), 91 (100); **HRMS** (FAB, THIOG) $[M+H]^+$ found 568.2552, $C_{32}H_{42}NO_4S_2$ requires 568.2555.

Method B: General procedure A was followed with thiolpropionate ester **131** (1.0 g, 2.0 mmol), dicyclohexylboron triflate (1.0 M in hexane, 4.4 ml, 4.4 mmol), triethylamine (0.67 ml, 4.8 mmol) and isobutyraldehyde (0.46 ml, 5.0 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137c** and **138c** that was separated by **HPLC** (1.08 mg, 94%) ($ds_{anti\,:\,anti}$ = 92 : 8, $ds_{anti\,:\,syn}$ = 99 : 1).

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-2,5-dimethyl-3-hydroxy-thiolhexanoate 137d



137d **138d**

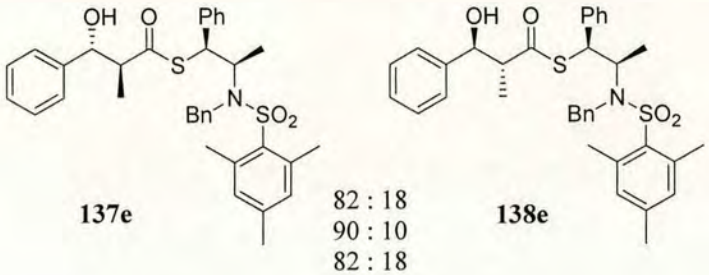
General procedure A was followed with thiolpropionate ester **131** (200 mg, 0.404 mmol), dibutylboron triflate (1.0 M in hexane, 0.81 ml, 0.81 mmol), diisopropylethylamine (0.21 ml, 1.2 mmol) and isovaleraldehyde (0.11 ml, 1.2 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137d** and **138d** that was separated by **HPLC** (197 mg, 84%) (ds $_{anti}$: $_{anti}$ = 77 : 23, ds $_{anti}$: $_{syn}$ = 99 : 1).

(2*S*,3*S*)-Major diastereoisomer 137d: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 72 min; R_f (20% EtOAc in hexane) = 0.36; $[\alpha]_D$ = + 70 (c 0.50, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3528 (OH), 1682 (C=O), 1321(SO_2N), 1152 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.48 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.40 – 7.27 (3H, m, Ar*H*), 7.23 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.10 (2H, t, *J* = 7.7 Hz, Ar*H*), 6.89 (2H, s, Ar*H*), 6.74 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.89 (1H, d, *J* = 9.0 Hz, C*H*Ph), 4.84 (1H, d, *J* = 16.2 Hz, C$H_A$$H_B$Ph), 4.54 (1H, d, *J* = 16.2 Hz, C$H_A$$H_B$Ph), 4.23 (1H, dq, *J* = 9.0 & 6.8 Hz, C(2')*H*CH_3), 3.78 (1H, ddd, *J* = 9.7, 6.2 & 3.4 Hz, C*H*OH), 2.68 (1H, dq, *J* = 7.1 & 6.2 Hz, C*H*CH_3), 2.37 (6H, s, 2 × *o*-CH_3), 2.36 (3H, s, *p*-CH_3), 1.95-1.79 (1H, m, C*H*$(CH_3)_2$), 1.40 (1H, ddd, *J* = 13.9, 9.7 & 4.6 Hz, C$H_E$$H_F$), 1.25 (1H, ddd, *J* = 13.9, 9.3 & 3.4 Hz, C$H_E$$H_F$), 1.36 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.16 (3H, d, *J* = 7.1 Hz, CHCH_3), 0.97 (3H, d, *J* = 6.6 Hz, CH(CH_3)$_A$$(CH_3)_B$), 0.93 (3H, d, *J* = 6.6 Hz, CH$(CH_3)_A$(CH_3)$_B$); **^{13}C NMR** δ (90.5 MHz, CDCl3) 201.47 (C), 142.75 (C), 140.95 (2 × C), 140.15 (C), 138.76 (C), 133.20 (C), 132.52 (2 × CH), 129.09 (2 × CH), 128.85 (2 × CH), 128.75 (2 × CH), 127.92 (2 × CH), 127.80 (CH), 127.63 (CH), 72.36 (CH), 57.09 (CH), 54.82 (CH), 51.59 (CH), 47.79 (CH_2), 44.31 (CH_2), 24.81 (CH), 23.99 (CH_3), 23.28 (2 × CH_3), 21.94 (CH_3), 21.29 (CH_3), 17.74 (CH_3), 15.02 (CH_3); ***m/z*** (FAB, 3-NOBA) 582 ($[M+H]^+$, 80%), 406 (69),

317 (93), 289 (62), 241 (83), 183 (80), 154 (100); **HRMS** (FAB, THIOG) $[M+H]^+$ found 582.2713, $C_{33}H_{44}NO_4S_2$ requires 582.2712.

(2*R*,3*R*)-Minor diastereoisomer 138d: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 84 min; R_f (20% EtOAc in hexane) = 0.33; $[\alpha]_D$ = + 40 (c 0.20, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3526 (OH), 1681 (C=O), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.63 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.55 – 7.40 (3H, m, Ar*H*), 7.34 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.23 (2H, t, *J* = 7.7 Hz, Ar*H*), 7.03 (2H, s, Ar*H*), 6.91 (2H, d, *J* = 7.1 Hz, Ar*H*), 5.00 (1H, d, *J* = 16.2 Hz, C$H_A$$H_B$Ph), 5.00 (1H, d, *J* = 8.9 Hz, C*H*Ph), 4.65 (1H, d, *J* = 16.2 Hz, C$H_A$$H_B$Ph), 4.35 (1H, dq, *J* = 8.9 & 6.8 Hz, C*H*CH_3), 3.86 (1H, ddd, *J* = 9.5, 5.8 & 3.5 Hz, C*H*OH), 2.80 (1H, dq, *J* = 7.1 & 5.8 Hz, C*H*CH_3), 2.51 (6H, s, 2 × *o*-CH_3), 2.50 (3H, s, *p*-CH_3), 2.10-1.80 (2H, br m, O*H* & C*H*$(CH_3)_2$), 1.45 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.35 (3H, d, *J* = 7.1 Hz, CHCH_3), 1.45-1.20 (2H, m, CHCH_2), 1.03 (3H, d, *J* = 6.6 Hz, CH(CH_3)$_A$$(CH_3)_B$), 0.97 (3H, d, *J* = 6.6 Hz, CH$(CH_3)_A$(CH_3)$_B$); **^{13}C NMR** δ (90.5 MHz, CDCl3) 201.01 (C), 142.26 (C), 140.41 (2 × C), 139.66 (C), 138.31 (C), 132.65 (C), 132.03 (2 × CH), 128.44 (2 × CH), 128.29 (2 × CH), 128.27 (2 × CH), 127.42 (2 × CH), 127.28 (CH), 127.12 (CH), 71.89 (CH), 56.35 (CH), 54.01 (CH), 51.21 (CH), 47.39 (CH_2), 43.59 (CH_2), 24.20 (CH), 23.36 (CH_3), 22.80 (2 × CH_3), 21.32 (CH_3), 20.81 (CH_3), 17.24 (CH_3), 14.70 (CH_3); ***m/z*** (FAB, 3-NOBA) 582 ($[M+H]^+$, 61%), 406 (62), 316 (98), 289 (35), 241 (70), 183 (69), 119 (90), 91 (99); **HRMS** (FAB, THIOG) $[M+H]^+$ found 582.2716, $C_{33}H_{44}NO_4S_2$ requires 582.2712.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-hydroxy-2-methyl-3-phenylthiolpropionate 137e



137e 82 : 18 **138e**

90 : 10
82 : 18
52 : 48
49 : 51
80 : 20
81 : 19
85 : 15

Method A: General procedure A was followed with thiolpropionate ester **131** (200 mg, 0.404 mmol), dibutylboron triflate (1.0 M in hexane, 0.81 ml, 0.81 mmol), diisopropylethylamine (0.21 ml, 1.2 mmol) and benzaldehyde (0.12 ml, 1.2 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137e** and **138e** that was separated by **HPLC** (215 mg, 88%) (ds $_{anti\ :\ anti}$ = 82 : 18, ds $_{anti\ :\ syn}$ = 98 : 2).

(2*S*,3*R*)-Major diastereoisomer 137e: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 78 min; R_t (20% EtOAc in hexane, flow rate: 10 ml/min) = 16 min; R_f (20% EtOAc in hexane) = 0.38; $[\alpha]_D$ = + 108 (c 7.85, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3509 (OH), 1683 (C=O), 1603 (Ar), 1494 (Ar), 1152 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.63 - 7.48 (8H, m, Ar*H*), 7.42 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.30 (2H, t, *J* = 7.7 Hz, Ar*H*), 7.10 (2H, s, Ar*H*), 6.92 (2H, d, *J* = 7.1 Hz, Ar*H*), 5.10 (1H, d, *J* = 8.8 Hz, C*H*Ph), 5.04 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 5.01 (1H, dd, *J* = 8.0 & 4.7 Hz, C*H*OH), 4.72 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.41 (1H, dq, *J* = 8.8 & 6.8 Hz, C(2')*H*CH_3), 3.18 (1H, dq, *J* = 8.0 & 7.1 Hz, C*H*CH_3), 2.92 (1H, d, *J* = 4.7 Hz, O*H*), 2.58 (6H, s, 2 × *o*-C*H*$_3$), 2.57 (3H, s, *p*-C*H*$_3$), 1.48 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 1.18 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 200.53 (C), 142.14 (C), 141.34 (C), 140.38 (2 × C), 139.59 (C), 138.35 (C), 132.69 (C), 131.94 (2 × CH), 128.54 (2 × CH), 128.32 (4 × CH), 128.26 (2 × CH), 128.15 (CH), 127.91 (2 × CH), 127.33 (CH), 127.17 (CH), 126.23 (2 × CH), 76.38 (CH), 56.68 (CH), 55.29 (CH),

51.07 (CH), 47.12 (CH_2), 22.70 (2 × CH_3), 20.72 (CH_3), 16.93 (CH_3), 14.87 (CH_3); ***m/z*** (FAB, THIOG) 602 ($[M+H]^+$, 74%), 406 (65), 316 (70), 288 (31), 195 (43), 183 (55), 119 (85), 91 (100); **HRMS** (FAB, THIOG) $[M+H]^+$ found 602.2397, $C_{35}H_{40}NO_4S_2$ requires 602.2399.

(2*R*,3*S*)-Minor diastereoisomer 138e: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 96 min; R_t (20% EtOAc in hexane, flow rate: 10 ml/min) = 18 min; R_f (20% EtOAc in hexane) = 0.34; $[\alpha]_D$ = - 6.4 (c 2.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3512 (OH), 1684 (C=O), 1603 (Ar), 1494 (Ar), 1152 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.36 (2H, d, *J* = 7.6 Hz, Ar*H*), 7.30 - 7.02 (9H, m, Ar*H*), 6.94 (2H, t, *J* = 7.7 Hz, Ar*H*), 6.75 (2H, s, Ar*H*), 6.61 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.76 (1H, d, *J* = 8.9 Hz, C*H*Ph), 4.73 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.66 (1H, dd, *J* = 8.3 & 3.7 Hz, C*H*OH), 4.38 (1H, d, *J* = 16.3 Hz, $CH_A\mathit{H}_B$Ph), 4.10 (1H, dq, *J* = 8.9 & 6.8 Hz, C(2')*H*CH_3), 2.80 (1H, dq, *J* = 8.3 & 7.1 Hz, C*H*CH_3), 2.38 (1H, br d, *J* = 3.7 Hz, O*H*), 2.23 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 1.19 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.85 (3H, d, *J* = 7.1 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 200.96 (C), 142.74 (C), 141.54 (C), 140.95 (2 × C), 140.02 (C), 138.86 (C), 133.22 (C), 132.53 (2 × CH), 129.03 (2 × CH), 128.83 (4 × CH), 128.78 (2 × CH), 128.51 (CH), 128.00 (2 × CH), 127.78 (CH), 127.59 (CH), 126.89 (2 × CH), 76.85 (CH), 57.07 (CH), 55.91 (CH), 51.72 (CH), 47.88 (CH_2), 23.28 (2 × CH_3), 21.30 (CH_3), 17.65 (CH_3), 15.49 (CH_3); ***m/z*** (FAB, THIOG) 602 ($[M+H]^+$, 74%), 406 (65), 289 (15), 195 (43), 183 (55), 163 (52), 119 (85), 91 (100), 77 (69); ***m/z*** (FAB, THIOG) 602 ($[M+H]^+$, 45%), 406 (57), 316 (63), 290 (55), 195 (30), 183 (47), 91 (90); **HRMS** (FAB, THIOG) $[M+H]^+$ found 602.2387, $C_{35}H_{40}NO_4S_2$ requires 602.2399.

Method B: General procedure A was followed with thiolpropionate ester **131** (150 mg, 0.303 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.91 ml, 0.91 mmol) and diisopropylethylamine (0.13 ml, 0.76 mmol). The reaction mixture was stirred at – 78 °C for 45 min, then benzaldehyde was added (97 μl, 0.91 mmol). The reaction was stirred at – 78 °C for 2.5 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137e** and **138e** that was separated by **HPLC** (157 mg, 86%) (ds $_{anti\,:\,anti}$ = 90 : 10, ds $_{anti\,:\,syn}$ = 99 : 1).

Method C: General procedure A was followed with thiolpropionate ester **131** (60 mg, 0.12 mmol), 9-BBN-triflate (0.5 M in hexane, 0.72 ml, 0.36 mmol) and diisopropylethylamine (53 µl, 0.30 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (38 µl, 0.36 mmol). The reaction was stirred at – 78 °C for 1.5 h and warmed to 0 °C for 1 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137e** and **138e** that was separated by **HPLC** (59 mg, 81%) (ds $_{anti\,:\,anti}$ = 82 : 18, ds $_{anti\,:\,syn}$ = 84 : 16).

Method D: A solution of diethylboron triflate was generated *in situ* by dropwise addition of triflic acid (55 µl, 0.61 mmol) to triethylborane (1.0 M in hexane, 0.61 ml, 0.61 mmol). The solution was stirred at RT for 20 min and then cooled to – 78 °C. A solution of thiolpropinate ester **131** (100 mg, 0.202 mmol) at – 78 °C in CH_2Cl_2 (10 ml) was added followed by diisopropylethylamine (87 µl, 0.61 mmol). The reaction mixture was stirred at – 78 °C for 30 min, then benzaldehyde was added (65 µl, 0.61 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. The mixture was quenched and extracted as described in **general procedure A**. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137e** and **138e** that was separated by **HPLC** (102 mg, 84%) (ds $_{anti\,:\,anti}$ = 80 : 20, ds $_{anti\,:\,syn}$ = 91 : 9).

Method E: General procedure A was followed with thiolpropionate ester **131** (150 mg, 0.303 mmol) in CH_2Cl_2 (15 ml) at 0 °C, to which was added dibutylboron triflate (1.0 M in hexane, 0.91 ml, 0.91 mmol) then diisopropylethylamine (0.13 ml, 0.76 mmol). The reaction mixture was stirred at 0 °C for 45 min, then benzaldehyde was added (97 µl, 0.91 mmol). The reaction was stirred at 0 °C for 2 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137e** and **138e** that was separated by **HPLC** (155 mg, 85%) (ds $_{anti\,:\,anti}$ = 81 : 19, ds $_{anti\,:\,syn}$ = 94 : 6, ds $_{syn\,:\,syn}$ = 51 : 49).

Method F: General procedure A was followed with thiolpropionate ester **131** (150 mg, 0.303 mmol) in CH_2Cl_2 (15 ml) at 0 °C, to which was added dicyclohexylboron triflate (1.0 M in hexane, 0.91 ml, 0.91 mmol) then triethylamine (0.11 ml, 0.76 mmol). The reaction mixture was stirred at 0 °C for 1 h, then benzaldehyde was added (97 µl, 0.91 mmol). The reaction was stirred at 0 °C for 1 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137e** and **138e** that was separated by **HPLC** (158 mg, 87%) (ds $_{anti\,:\,anti}$ = 82 : 18, ds $_{anti\,:\,syn}$ = 95 : 5, ds $_{syn\,:\,syn}$ = 65 : 35).

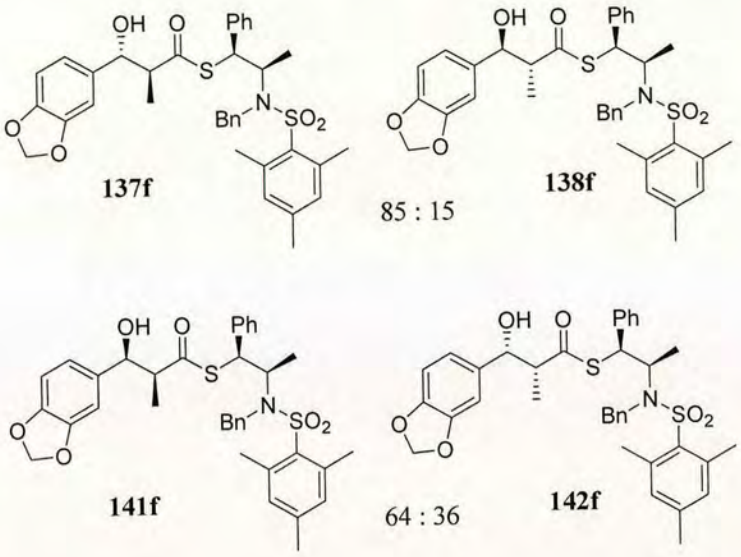
Method G: General procedure A was followed with thiolpropionate ester **131** (60 mg, 0.12 mmol) in CH_2Cl_2 (6 ml) at RT, to which was added dibutylboron triflate (1.0 M in hexane, 0.36 ml, 0.36 mmol) then diisopropylethylamine (53 µl, 0.30 mmol). The reaction mixture was stirred at RT for 1 h, then benzaldehyde was added (39 µl, 0.36 mmol). The reaction was stirred at RT for 2 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137e** and **138e** that was separated by **HPLC** (60 mg, 82%) (ds $_{anti\,:\,anti}$ = 52 : 48, ds $_{anti\,:\,syn}$ = 83 : 13, ds $_{syn\,:\,syn}$ = 73 : 27).

Method H: General procedure A was followed with thiolpropionate ester **131** (60 mg, 0.12 mmol) in CH_2Cl_2 (6 ml) at RT, to which was added dicyclohexylboron triflate (1.0 M in hexane, 0.36 ml, 0.36 mmol) then triethylamine (43 µl, 0.30 mmol). The reaction mixture was stirred at RT for 1 h, then benzaldehyde was added (39 µl, 0.36 mmol). The reaction was stirred at RT for 2 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137e** and **138e** that was separated by **HPLC** (52 mg, 71%) (ds $_{anti\,:\,anti}$ = 49 : 51, ds $_{anti\,:\,syn}$ = 96 : 4, ds $_{syn\,:\,syn}$ = 99 : 1).

Method I: General procedure A was followed with thiolpropionate ester **131** (150 mg, 0.303 mmol) in CH_2Cl_2 (15 ml) at – 78 °C, to which was added dicyclohexylboron chloride (0.20 ml, 0.91 mmol) then triethylamine (0.11 ml, 0.76 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (97 µl, 0.91 mmol). The reaction was stirred at – 78 °C for 1.5 h and warmed to 0 °C for 1 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137e** and **138e** that was separated by **HPLC** (168 mg, 92%) (ds $_{anti\,:\,anti}$ = 90 : 10, ds $_{anti\,:\,syn}$ = 97 : 3).

Method J: General procedure A was followed with thiolpropionate ester **131** (150 mg, 0.303 mmol) in diethylether (15 ml) at – 78 °C, to which was added dicyclohexylboron chloride (0.20 ml, 0.91 mmol) then triethylamine (0.11 ml, 0.76 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (97 µl, 0.91 mmol). The reaction was stirred at – 78 °C for 1.5 h and warmed to 0 °C for 1 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137e** and **138e** that was separated by **HPLC** (149 mg, 82%) ($ds_{anti:anti}$ = 85 : 15, $ds_{anti:syn}$ = 98 : 2).

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-hydroxy-2-methyl-3-piperonylthiolpropionate 137f



General procedure A was followed with thiolpropionate ester **131** (725 mg, 1.46 mmol), dibutylboron triflate (1.0 M in hexane, 2.94 ml, 2.94 mmol), diisopropylethylamine (0.76 ml, 4.4 mmol) and piperonal (0.65 g, 4.4 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **137f**, **138f**, **141f** and **142f** that was separated by **HPLC** (755 mg, 80%) (ds $_{anti\,:\,anti}$ = 85 : 15, ds $_{syn\,:\,syn}$ = 64 : 36, ds $_{anti\,:\,syn}$ = 97 : 3).

(2*S*,3*R*)-Major *anti* diastereoisomer 137f: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 63 min; R_f (20% EtOAc in hexane) = 0.24; $[\alpha]_D$ = + 99 (c 1.1, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3467 (OH), 1682 (C=O), 1154 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.35 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.26 - 7.15 (3H, m, Ar*H*), 7.08 (1H, t, *J* = 7.4 Hz, Ar*H*), 6.96 (2H, t, *J* = 7.6 Hz, Ar*H*), 6.75 (3H, d, *J* = 8.4 Hz, Ar*H*), 6.65 (2H, s, Ar*H*), 6.58 (2H, d, *J* = 7.0 Hz, Ar*H*), 5.86 (1H, d, *J* = 1.4 Hz, CH_CH$_D$O), 5.85 (1H, d, *J* = 1.4 Hz, CH$_C$$H_D$O), 4.75 (1H, d, *J* = 8.5 Hz, C*H*Ph), 4.64 (1H, d, *J* = 16.3 Hz, CH_AH$_B$Ph), 4.60 (1H, d, *J* = 8.3 Hz, C*H*OH), 4.39 (1H, d, *J* = 16.3 Hz, CH$_A$$H_B$Ph), 4.09 (1H, dq, *J* = 8.5 & 6.7 Hz, C(2')*H*CH$_3$), 2.77 (1H, dq, *J* = 8.3 & 7.1 Hz, C*H*CH$_3$), 2.24 (6H, s, 2 × *o*-CH_3), 2.23 (3H, s, *p*-CH_3), 1.17 (3H, d, *J* = 6.7 Hz, CHCH_3), 0.82 (3H, d, *J* = 7.1 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 201.05 (C), 148.28 (C), 147.77 (C), 142.73 (C), 140.97 (2 × C), 140.19 (C), 138.93 (C), 135.91 (C), 133.29 (C), 132.52 (2 × CH),

129.09 (2 × CH), 128.84 (2 × CH), 128.74 (2 × CH), 127.92 (2 × CH), 127.75 (CH), 127.62 (CH), 120.53 (CH), 108.46 (CH), 106.99 (CH), 101.49 (CH_2), 76.84 (CH), 57.29 (CH), 55.98 (CH), 51.72 (CH), 47.70 (CH_2), 23.29 (2 × CH_3), 21.30 (CH_3), 17.48 (CH_3), 15.45 (CH_3); ***m/z*** (FAB, 3-NOBA) 644 ($[M-H]^+$, 99%), 406 (92), 289 (54), 207 (76), 183 (57), 119 (90), 91 (100); **HRMS** (FAB, 3-NOBA) $[M-H]^+$ found 644.2141, $C_{36}H_{38}NO_6S_2$ requires 644.2141.

(2*R*,3*S*)-Minor *anti* diastereoisomer 138f: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 68 min; **R_f** (20% EtOAc in hexane) = 0.20; **$[\alpha]_D$** = - 8.3 (c 0.60, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3510 (OH), 1684 (C=O), 1152 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.35 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.26 - 7.15 (3H, m, Ar*H*), 7.07 (1H, t, *J* = 7.4 Hz, Ar*H*), 6.95 (2H, t, *J* = 7.7 Hz, Ar*H*), 6.76 (2H, s, Ar*H*), 6.66-6.57 (5H, m, Ar*H*), 5.85 (2H, s, CH_2O), 4.76 (1H, d, *J* = 9.0 Hz, C*H*Ph), 4.68 (1H, d, *J* = 16.3 Hz, C$H_A$$H_B$Ph), 4.59 (1H, d, *J* = 8.5 Hz, C*H*OH), 4.38 (1H, d, *J* = 16.3 Hz, CH$_A$$H_B$Ph), 4.10 (1H, dq, *J* = 9.0 & 6.8 Hz, C(2')*H*CH_3), 2.76 (1H, dq, *J* = 8.5 & 7.2 Hz, C*H*CH_3), 2.23 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 1.18 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.85 (3H, d, *J* = 7.2 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 201.63 (C), 148.87 (C), 148.41 (C), 143.41 (C), 141.61 (2 × C), 140.61 (C), 139.50 (C), 136.15 (C), 133.79 (C), 133.19 (2 × CH), 129.68 (2 × CH), 129.49 (2 × CH), 129.45 (2 × CH), 128.63 (2 × CH), 128.45 (CH), 128.27 (CH), 121.27 (CH), 109.08 (CH), 107.68 (CH), 102.12 (CH_2), 77.30 (CH), 57.73 (CH), 56.62 (CH), 52.31 (CH), 48.52 (CH_2), 23.95 (2 × CH_3), 21.98 (CH_3), 18.29 (CH_3), 16.16 (CH_3); ***m/z*** (FAB, THIOG) 646 ($[M+H]^+$, 10%), 464 (23), 406 (47), 316 (40), 207 (37), 183 (31), 119 (50), 91 (72); **HRMS** (FAB, THIOG) $[M+H]^+$ found 646.2297, $C_{36}H_{40}NO_6S_2$ requires 646.2297.

(2*S*,3*S*)-Major *syn* diastereoisomer 141f: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 74 min; **R_f** (20% EtOAc in hexane) = 0.18; **$[\alpha]_D$** = + 89 (c 0.45, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3465 (OH), 1682 (C=O), 1154 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.35-7.28 (2H, m, Ar*H*), 7.26 - 7.15 (3H, m, Ar*H*), 7.08 (1H, t, *J* = 7.4 Hz, Ar*H*), 6.94 (2H, t, *J* = 7.7 Hz, Ar*H*), 6.74 (3H, d, *J* = 8.4 Hz, Ar*H*), 6.62 (2H, s, Ar*H*), 6.58 (2H, d, *J* = 7.6 Hz, Ar*H*), 5.81 (1H, d, *J* = 1.4 Hz, C$H_C$$H_D$O), 5.80 (1H, d, *J* = 1.4 Hz, CH$_C$$H_D$O), 4.76 (1H, d, *J* = 5.9 Hz, C*H*OH), 4.64 (1H, d, *J* = 16.3 Hz, C$H_A$$H_B$Ph), 4.62 (1H, d, *J* = 8.5 Hz, C*H*Ph), 4.28 (1H, d, *J* = 16.3 Hz, CH$_A$$H_B$Ph), 4.00 (1H, dq, *J* = 8.5 & 6.9 Hz, C(2')*H*CH_3), 2.72 (1H, dq, *J* = 6.8 & 5.9 Hz, C*H*CH_3), 2.22 (3H, s, *p*-CH_3),

2.18 (6H, s, 2 × *o*-CH_3), 1.03 (3H, d, *J* = 6.9 Hz, CHCH_3), 0.97 (3H, d, *J* = 6.8 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 200.99 (C), 148.69 (C), 148.16 (C), 143.45 (C), 141.60 (2 × C), 140.80 (C), 139.51 (C), 136.22 (C), 133.77 (C), 133.19 (2 × CH), 129.71 (2 × CH), 129.51 (CH), 129.41 (2 × CH), 128.50 (2 × CH), 128.46 (2 × CH), 128.30 (CH), 120.82 (CH), 109.13 (CH), 107.77 (CH), 102.08 (CH_2), 75.41 (CH), 57.53 (CH), 56.84 (CH), 52.26 (CH), 48.37 (CH_2), 23.92 (2 × CH_3), 21.98 (CH_3), 18.07 (CH_3), 13.74 (CH_3); ***m/z*** (FAB, THIOG) 646 ([M+H]$^+$, 10%), 464 (31), 406 (47), 207 (37), 183 (31), 119 (50), 91 (72), 77 (47); ***m/z*** (FAB, THIOG) 646 ([M-H]$^+$, 18%), 406 (59), 316 (54), 207 (45), 91 (91); **HRMS** (FAB, THIOG) [M+H]$^+$ found 646.2296, $C_{36}H_{40}NO_6S_2$ requires 646.2297.

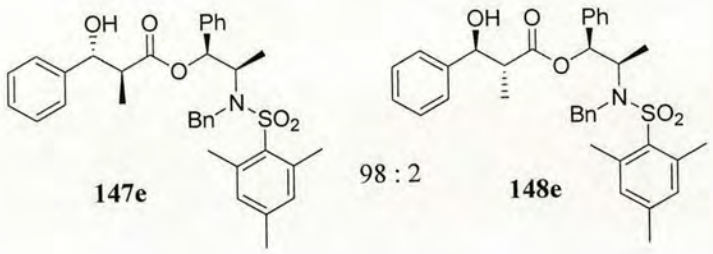
(2*R*,3*R*)-Minor *syn* diastereoisomer 142f: HPLC R_t (10% EtOAc in hexane, flow rate: 5 ml/min) = 58 min; **R_f** (20% EtOAc in hexane) = 0.20; **$[\alpha]_D$** = - 20 (c 0.15, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3466 (OH), 1709 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.35-7.28 (2H, m, Ar*H*), 7.27-7.12 (3H, m, Ar*H*), 7.11 - 7.04 (1H, m, Ar*H*), 6.95 (2H, t, *J* = 7.2 Hz, Ar*H*), 6.75 (2H, s, Ar*H*), 6.65 (1H, s, Ar*H*), 6.58-6.52 (4H, m, Ar*H*), 5.82 (1H, d, *J* = 1.4 Hz, CH_CH$_D$O), 5.81 (1H, d, *J* = 1.4 Hz, CH$_C$$H_D$O), 4.78 (1H, d, *J* = 4.4 Hz, C*H*OH), 4.69 (1H, d, *J* = 16.2 Hz, CH_AH$_B$Ph), 4.68 (1H, d, *J* = 9.1 Hz, C*H*Ph), 4.35 (1H, d, *J* = 16.2 Hz, CH$_A$$H_B$Ph), 4.10 (1H, dq, *J* = 9.1 & 6.8 Hz, C(2')*H*CH$_3$), 2.68 (1H, dq, *J* = 7.1 & 4.4 Hz, C*H*CH$_3$), 2.22 (9H, s, 3 × *o*-CH_3 & *p*-CH_3), 1.17 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.06 (3H, d, *J* = 7.1 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 201.84 (C), 148.54 (2 × C), 143.44 (C), 141.60 (2 × C), 140.66 (C), 139.40 (C), 135.84 (C), 133.75 (C), 133.19 (2 × CH), 129.67 (2 × CH), 129.45 (4 × CH), 128.58 (2 × CH), 128.47 (CH), 128.28 (CH), 120.33 (CH), 109.01 (CH), 107.54 (CH), 101.97 (CH_2), 74.60 (CH), 57.48 (CH), 56.21 (CH), 52.30 (CH), 48.46 (CH_2), 23.94 (2 × CH_3), 21.98 (CH_3), 18.33 (CH_3), 12.63 (CH_3); ***m/z*** (FAB, THIOG) 646 ([M-H]$^+$, 19%), 464 (13), 406 (44), 386 (43), 316 (42), 207 (43), 183 (27), 119 (51), 91 (81); **HRMS** (FAB, 3-NOBA) [M+H]$^+$ found 646.2300, $C_{36}H_{40}NO_6S_2$ requires 646.2297.

General procedure B: Synthesis of Masamune *Anti* Propionate Aldol Adducts

To a stirred solution of Masamune propionate ester **ent-134** (60 mg, 0.13 mmol) in CH_2Cl_2 (6 ml) at - 78 °C was added dicyclohexylboron triflate (1.0 M in hexane, 0.29 ml, 0.29 mmol) then triethylamine (44 µl, 0.31 mmol). The reaction mixture was stirred at – 78 °C for 1.5 h, then benzaldehyde was added (42 µl, 0.39 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. The mixture was quenched by the addition of pH 7 buffer and methanol (1:1, 3 ml) and diluted with methanol (6 ml) to make a homogeneous solution. After careful addition of H_2O_2 (30%, 1.5 ml) the mixture was stirred at RT for 18 h.

NaCl (10 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The combined organics were washed with $NaHCO_3$ (10 ml, sat aq) and NaCl (10 ml, sat aq), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldol product. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **147e** and **148e** that was separated by **HPLC**.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-hydroxy-2-methyl-3-phenypropionate 147e



General procedure B was followed with Masamune propionate ester **ent-134** (60 mg, 0.13 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.29 ml, 0.29 mmol), triethylamine (44 µl, 0.31 mmol) and benzaldehyde (42 µl, 0.39 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **147e** and **148e** that was separated by **HPLC** (68 mg, 93%) (ds $_{anti:syn}$ > 99 : 1, ds $_{anti:anti}$ = 98 : 2).

(2*S*,3*R*)-Major *anti* diastereoisomer 147e: HPLC R_t (15% EtOAc in hexane, flow rate: 10 ml/min) = 26 min; **R_f** (20% EtOAc in hexane) = 0.29; **$[\alpha]_D$** = - 18.8 (c 1.70, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3510 (OH), 1740 (CO), 1603 (Ar), 1495 (Ar), 1320 (SO_2N), 1151 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.33-7.05 (13H, m, Ar*H*), 6.82 (2H, s, Ar*H*), 6.78 – 6.70 (2H, m, Ar*H*), 5.74 (1H, d, *J* = 3.8 Hz, C*H*Ph), 4.67 (1H, d, *J* = 16.6 Hz, CH_AH_BPh), 4.63 (1H, d, *J* = 8.3 Hz, C*H*OH), 4.42 (1H, d, *J* = 16.6 Hz, CH_AH_BPh), 3.97 (1H, dq, *J* = 7.0 & 3.8 Hz, C(2')*H*CH_3), 2.96 (1H, br s, O*H*), 2.70 (1H, dq, *J* = 8.3 & 7.2 Hz, C*H*CO), 2.43 (6H, s, *o*-CH_3), 2.21 (3H, s, *p*-CH_3), 1.03 (3H, d, *J* = 7.0 Hz, CHCH_3), 0.87 (3H, d, *J* = 7.2 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 175.65 (C), 143.63 (C), 142.54 (C), 141.33 (2 × C), 139.81 (C), 139.24 (C), 134.50 (C), 133.18 (2 × CH), 129.60 (2 × CH), 129.47 (2 × CH), 129.36 (2 × CH), 129.17 (CH), 128.96 (CH), 128.67 (2 × CH), 128.17 (CH), 127.69 (2 × CH), 126.83 (2 × CH), 79.50 (CH), 77.38 (CH), 57.83 (CH), 49.26 (CH_2), 48.29 (CH), 23.98 (2 × CH_3), 21.93 (CH_3), 15.52 (CH_3), 14.24 (CH_3); ***m/z*** (ESI, +) 603 ($[M+NH_4]^+$, 100%), 586 ($[M+H]^+$, 20), 406 (67); **HRMS** (ESI, +) $[M+NH_4]^+$ found 603.2887, $C_{35}H_{43}N_2O_5S$ requires 603.2887.

(2*R*,3*S*)-Minor *anti* diastereoisomer 148e: HPLC R_t (15% EtOAc in hexane, flow rate: 10 ml/min) = 29 min; **R_f** (20% EtOAc in hexane) = 0.25; **^{1}H NMR** δ (250 MHz,

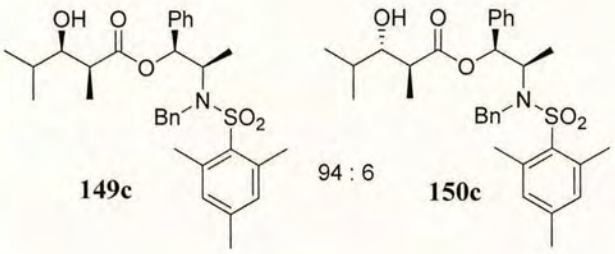
$CDCl_3$) 7.33-7.05 (13H, m, Ar*H*), 6.79 (2H, s, Ar*H*), 6.78 – 6.73 (2H, m, Ar*H*), 5.79 (1H, d, J = 4.1 Hz, C*H*Ph), 4.70 (1H, d, J = 16.6 Hz, CH_AH$_B$Ph), 4.67-4.60 (1H, m, C*H*OH), 4.42 (1H, d, J = 16.6 Hz, CH$_A$$H_B$Ph), 4.05 (1H, dq, J = 6.9 & 4.1 Hz, C(2')*H*CH_3), 2.75 (1H, qn, J = 7.2 Hz, C*H*CO), 2.43 (6H, s, *o*-CH_3), 2.20 (3H, s, *p*-CH_3), 1.11 (3H, d, J = 7.0 Hz, CHCH_3), 0.89 (3H, d, J = 7.2 Hz, CHCH_3).

General procedure C: Synthesis of Masamune *Syn* Propionate Aldol Adducts

To a stirred solution of Masamune propionate ester **ent-134** (150 mg, 0.320 mmol) in CH_2Cl_2 (10 ml) at – 78 °C was added dibutylboron triflate (1.0 M in hexane, 0.63 ml, 0.63 mmol) then diisopropylethylamine (0.17 ml, 0.96 mmol). The reaction mixture was stirred at – 78 °C for 2 h, then aldehyde was added (0.47 mmol). The reaction was stirred at – 78 °C for 1.5 h and warmed to 0 °C for 1 h. The mixture was quenched by the addition of pH 7 buffer and methanol (1:1, 4 ml) and diluted with methanol (6 ml) to make a homogeneous solution. After careful addition of H_2O_2 (30%, 2 ml) the mixture was stirred at RT for 18 h.

NaCl (30 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 ml). The combined organics were washed with $NaHCO_3$ (30 ml, sat aq) and NaCl (30 ml, sat aq), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldol product. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereomeric aldol adducts.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-2,4-dimethyl-3-hydroxy-pentanoate 149c

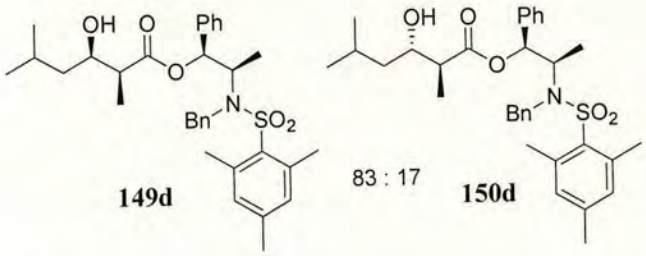


General procedure C was followed with Masamune propionate ester **ent-134** (150 mg, 0.320 mmol), dibutylboron triflate (1.0 M in hexane, 0.63 ml, 0.63 mmol), diisopropylethylamine (0.17 ml, 0.96 mmol) and isobutyraldehyde (43 μl, 0.47 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **149c** and **150c** (142 mg, 82%) (ds $_{syn\ :\ anti}$ = 94 : 6).

(2*S*,3*R*)-Major diastereoisomer 149c: R_f (20% EtOAc in hexane) = 0.32; $[\alpha]_D$ = - 10 (c 0.70, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3533 (OH), 1736 (CO), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.30-7.12 (8H, m, Ar*H*), 7.00-6.90 (2H, m, Ar*H*), 6.85 (2H, s, Ar*H*), 5.88 (1H, d, *J* = 3.7 Hz, C*H*Ph), 4.70 (1H, d, *J* = 16.7 Hz, CH_AH_BPh), 4.60 (1H, d, *J* = 16.7 Hz, CH_AH_BPh), 4.06 (1H, qd, *J* = 7.0 and 3.7 Hz, C(2')*H*CH_3), 3.38 (1H, dd, *J* = 8.5 & 3.0 Hz, C*H*OH), 2.50 (6H, s, *o*-CH_3), 2.40 (1H, qd, *J* = 7.2 & 3.0 Hz, C*H*CO), 2.24 (3H, s, *p*-CH_3), 1.56-1.52 (1H, m, $(CH_3)_2CH$), 1.14 (3H, d, *J* = 7.0 Hz, CH_3CHN), 1.10 (3H, d, *J* = 7.2 Hz, CH_3CHCO), 0.93 (3H, d, *J* = 6.6 Hz, $(CH_3)_2$CH), 0.77 (3H, d, *J* = 6.6 Hz, $(CH_3)_2$CH); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 175.93 (C), 143.62 (C), 141.22 (2 × C), 139.54 (C), 139.35 (C), 134.34 (C), 133.18 (2 × CH), 129.48 (4 × CH), 128.99 (CH), 128.13 (3 × CH), 126.88 (2 × CH), 79.45 (CH), 77.25 (CH), 57.86 (CH), 49.23 (CH_2), 42.60 (CH), 31.36 (CH), 24.04 (2 × CH_3), 21.90 (CH_3), 20.16 (CH_3), 19.91 (CH_3), 13.68 (CH_3), 10.45 (CH_3); ***m/z*** (FAB, 3-NOBA) 552 ($[M+H]^+$, 15%), 406 (82), 316 (76), 183 (18), 119 (81), 91 (100); **HRMS** (FAB, THIOG) $[M+H]^+$ found 552.2784, $C_{32}H_{42}NO_5S$ requires 552.2784.

(2*S*,3*S*)-Minor diastereoisomer 150c: R_f (20% EtOAc in hexane) = 0.43; $[\alpha]_D$ = - 20 (c 0.20, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3539 (OH), 1737 (CO), 1152 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.40-7.20 (8H, m, Ar*H*), 6.97-6.87 (4H, m, Ar*H*), 5.89 (1H, d, *J* = 4.4 Hz, C*H*Ph), 4.87 (1H, d, $J_{A\text{-}B}$ = 16.5 Hz, CH_AH_BPh), 4.63 (1H, d, $J_{A\text{-}B}$ = 16.5 Hz, CH_AH_BPh), 4.20 (1H, qd, *J* = 7.0 & 4.4 Hz, C(2')*H*CH_3), 3.48 (1H, dd, *J* = 7.2 & 4.5 Hz, C*H*OH), 2.70 (1H, qn, *J* = 7.2 Hz, C*H*CO), 2.57 (6H, s, *o*-CH_3), 2.36 (3H, s, *p*-CH_3), 1.81 (1H, sptd, *J* = 6.8 and 4.5 Hz, $(CH_3)_2CH$), 1.32 (3H, d, *J* = 7.0 Hz, CH_3CHN), 1.25 (3H, d, *J* = 7.2 Hz, CH_3CHCO), 1.04 (3H, d, *J* = 6.8 Hz, $(CH_3)_2$CH), 1.02 (3H, d, *J* = 6.8 Hz, $(CH_3)_2$CH); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 176.03 (C), 143.57 (C), 141.30 (2 × C), 139.57 (C), 139.21 (C), 134.42 (C), 133.14 (2 × CH), 129.43 (2 × CH), 129.34 (2 × CH), 128.97 (CH), 128.70 (2 × CH), 128.19 (CH), 126.98 (2 × CH), 79.23 (CH), 78.76 (CH), 57.76 (CH), 49.28 (CH_2), 44.03 (CH), 31.21 (CH), 23.95 (2 × CH_3), 21.91 (CH_3), 21.00 (CH_3), 16.63 (CH_3), 15.38 (CH_3), 14.62 (CH_3); ***m/z*** (FAB, 3-NOBA) 552 ($[M+H]^+$, 6%), 406 (80), 316 (78), 289 (31), 183 (52), 129 (50), 119 (84), 91 (95); **HRMS** (FAB, THIOG) $[M+H]^+$ found 552.2789, $C_{32}H_{42}NO_5S$ requires 552.2784.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-2,5-dimethyl-3-hydroxy-hexanoate 149d

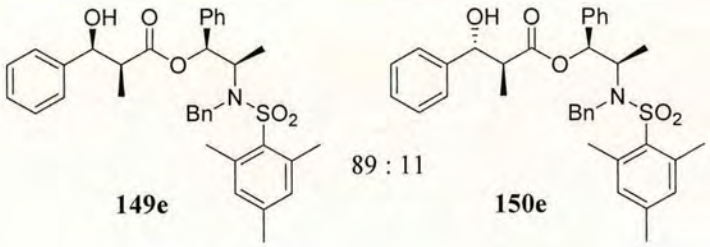


General procedure C was followed with Masamune propinate ester **ent-134** (150 mg, 0.320 mmol), dibutylboron triflate (1.0 M in hexane, 0.64 ml, 0.64 mmol), diisopropylethylamine (0.17 ml, 0.96 mmol) and isovaleraldehyde (53 μl, 0.48 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **149d** and **150d** (108 mg, 61%) (ds $_{syn\,:\,anti}$ = 83 : 17).

(2*S*,3*R*)-Major diastereoisomer 149d: R_f (20% EtOAc in hexane) = 0.25; $[\alpha]_D$ = - 3.0 (c 0.75, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3530 (OH), 1735 (CO), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.37-7.21 (8H, m, Ar*H*), 7.05-6.98 (2H, m, Ar*H*), 6.92 (2H, s, Ar*H*), 5.95 (1H, d, *J* = 3.7 Hz, C*H*Ph), 4.71 (1H, d, *J* = 17.0 Hz, CH_AH_BPh), 4.64 (1H, d, *J* = 17.0 Hz, CH_AH_BPh), 4.14 (1 H, qd, *J* = 7.0 & 3.7 Hz, C(2')*H*CH_3), 3.94-3.90 (1H, m, C*H*OH), 2.57 (6H, s, *o*-CH_3), 2.25 (1H, qd, *J* = 7.3 & 3.0 Hz, CH_3CHCO), 2.32 (3H, s, *p*-CH_3), 1.83-1.70 (1H, m, C*H*$(CH_3)_2$), 1.41 (1H, ddd, *J* = 13.7, 9.8 & 5.1 Hz, CH_CH_D), 1.23 (3H, d, *J* = 7.0 Hz, CH_3CHN), 1.20 (3H, d, *J* = 7.3 Hz, CH_3CHCO), 1.03 (1H, ddd, *J* = 13.7, 8.9 & 3.6 Hz, CH_CH_D), 0.92 (6H, d, *J* = 6.6 Hz, $(CH_3)_2CHCH_2$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 175.04 (C), 142.98 (C), 140.56 (2 × C), 138.86 (C), 138.70 (C), 133.66 (C), 132.53 (2 × CH), 128.84 (4 × CH), 128.79 (CH), 127.53 (3 × CH), 126.22 (2 × CH), 78.77 (CH), 69.43 (CH), 57.23 (CH), 48.60 (CH_2), 44.73 (CH), 42.91 (CH_2), 24.90 (CH), 23.85 (CH_3), 23.38 (2 × CH_3), 22.24 (CH_3), 21.25 (CH_3), 12.98 (CH_3), 10.57 (CH_3); ***m/z*** (FAB, 3-NOBA) 566 ($[M+H]^+$, 48%), 406 (86), 316 (81), 183 (55), 119 (84), 91 (94); **HRMS** (FAB, 3-NOBA) $[M-H]^+$ found 564.2789, $C_{33}H_{42}NO_5S$ requires 564.2784.

(2*S*,3*S*)-Minor diastereoisomer 150d: R_f (20% EtOAc in hexane) = 0.29; $[\alpha]_D$ = - 18 (c 0.45, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3529 (OH), 1731 (CO), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.25-7.08 (8H, m, Ar*H*), 6.85-6.80 (4H, m, Ar*H*), 5.76 (1H, d, *J* = 4.4 Hz, C*H*Ph), 4.68 (1H, d, *J* = 16.4 Hz, CH_AH_BPh), 4.46 (1H, d, *J* = 16.4 Hz, CH_AH_BPh), 4.04 (1H, qd, *J* = 6.9 and 4.4 Hz, C(2')*H*CH_3), 3.61-3.58 (1H, m, C*H*OH), 2.44-2.33 (1H, m, CH_3CHCO), 2.41 (6H, s, *o*-CH_3), 2.20 (3H, s, *p*-CH_3), 1.85-1.70 (1H, m, C*H*$(CH_3)_2$), 1.37-1.25 (1H, m, CH_CH_D), 1.18-1.00 (1H, m, CH_CH_D), 1.14 (3H, d, *J* = 6.9 Hz, CH_3CHN), 1.06 (3H, d, *J* = 7.3 Hz, CH_3CHCO), 0.86 (3H, d, *J* = 6.7 Hz, CH_3CHCH_2), 0.81 (3H, d, *J* = 6.5 Hz, CH_3CHCH_2); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 174.52 (C), 142.45 (C), 140.16 (2 × C), 138.30 (C), 138.01 (C), 133.23 (C), 132.00 (2 × CH), 128.31 (4 × CH), 127.88 (CH), 127.56 (3 × CH), 125.91 (2 × CH), 78.10 (CH), 71.24 (CH), 56.56 (CH), 48.14 (CH_2), 45.87 (CH), 43.63 (CH_2), 24.29 (CH), 23.63 (CH_3), 22.87 (2 × CH_3), 21.39 (CH_3), 20.78 (CH_3), 14.10 (CH_3), 13.46 (CH_3); ***m/z*** (FAB, 3-NOBA) 564 ($[M+H]^+$, 6%), 406 (30); **HRMS** (FAB, 3-NOBA) $[M-H]^+$ found 564.2781, $C_{33}H_{42}NO_5S$ requires 564.2784.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)-3-hydroxy-2-methyl-3-phenypropionate 149e



149e **150e**

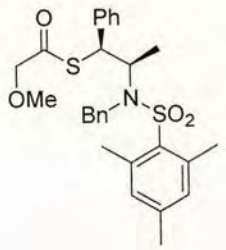
General procedure C was followed with Masamune propionate ester **ent-134** (188 mg, 0.392 mmol), dibutylboron triflate (1.0 M in hexane, 0.78 ml, 0.78 mmol), diisopropylethylamine (0.21 ml, 1.2 mmol) and benzaldehyde was added (63 µl, 0.59 mmol). The reaction was stirred at – 78 °C for 1 h and warmed to 0 °C for 1 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **149e** and **150e** that was separated by **HPLC** (192 mg, 84%) (ds *syn : anti* = 89 : 11).

(2*S*,3*S*)-Major diastereoisomer 149e: HPLC R_t (15% EtOAc in hexane, flow rate: 10 ml/min) = 28 min; **R_f** (20% EtOAc in hexane) = 0.18; **$[\alpha]_D$** = - 29 (c 1.0, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3513 (OH), 1737 (CO), 1603 (Ar), 1495 (Ar), 1323 (SO_2N), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.66-7.40 (13H, m, Ar*H*), 7.25 - 7.15 (2H, m, Ar*H*), 7.13 (2H, s, Ar*H*), 6.12 (1H, d, *J* = 3.5 Hz, C*H*Ph), 5.20 (1H, t, *J* = 3.6 Hz, C*H*OH), 4.85 (1H, d, *J* = 16.8 Hz, CH_AH_BPh), 4.75 (1H, d, *J* = 16.8 Hz, CH_AH_BPh), 4.28 (1H, qd, *J* = 7.0 & 3.5 Hz, C(2')*H*CH_3), 3.17 (1H, d, *J* = 3.4 Hz, O*H*), 2.85-2.70 (1H, m, C*H*CH_3), 2.77 (6H, s, *o*-CH_3), 2.52 (3H, s, *p*-CH_3), 1.35 (3H, d, *J* = 7.0 Hz, CHCH_3), 1.30 (3H, d, *J* = 7.2 Hz, CHCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 174.66 (C), 143.03 (C), 141.79 (C), 140.62 (2 × C), 139.00 (C), 138.62 (C), 133.70 (C), 132.57 (2 × CH), 128.88 (4 × CH), 128.68 (2 × CH), 128.37 (CH), 127.82 (CH), 127.65 (2 × CH), 127.56 (CH), 126.36 (2 × CH), 126.24 (2 × CH), 79.00 (CH), 73.24 (CH), 57.23 (CH), 48.58 (CH_2), 46.64 (CH), 23.42 (2 × CH_3), 21.28 (CH_3), 12.93 (CH_3), 10.95 (CH_3); ***m/z*** (ESI, +) 603 ($[M+NH_4]^+$, 100%), 586 ($[M+H]^+$, 30); **HRMS** (ESI, +) $[M+NH_4]^+$ found 603.2889, $C_{35}H_{43}N_2O_5S$ requires 603.2887.

(2*S*,3*R*)-Minor diastereoisomer 150e: HPLC R_t (15% EtOAc in hexane, flow rate: 10 ml/min) = 25 min; R_f (20% EtOAc in hexane) = 0.21; $[\alpha]_D$ = - 18 (c 0.90, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3509 (OH), 1740 (C=O), 1603 (Ar), 1495 (Ar), 1320 (SO_2N), 1151 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.35-7.00 (13H, m, Ar*H*), 6.82 (2H, s, Ar*H*), 6.78 – 6.70 (2H, m, Ar*H*), 5.75 (1H, d, *J* = 3.8 Hz, C*H*Ph), 4.67 (1H, d, *J* = 16.6 Hz, CH_AH_BPh), 4.64 (1H, dd, *J* = 8.3 & 4.4 Hz, C*H*OH), 4.42 (1H, d, *J* = 16.6 Hz, CH_AH_BPh), 4.00 (1H, qd, *J* = 7.0 & 3.8 Hz, C(2')*H*CH_3), 3.95 (1H, d, *J* = 4.4 Hz, O*H*), 2.70 (1H, dq, *J* = 8.3 & 7.2 Hz, C*H*CH_3), 2.43 (6H, s, *o*-CH_3), 2.23 (3H, s, *p*-CH_3), 1.04 (3H, d, *J* = 7.0 Hz, CHCH_3), 0.87 (3H, d, *J* = 7.2 Hz, CHCH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 174.99 (C), 142.97 (C), 141.90 (C), 140.70 (2 × C), 139.16 (C), 138.61 (C), 133.89 (C), 132.53 (2 × CH), 128.96 (2 × CH), 128.82 (2 × CH), 128.72 (2 × CH), 128.53 (CH), 128.32 (CH), 128.05 (2 × CH), 127.53 (CH), 127.05 (2 × CH), 126.21 (2 × CH), 78.86 (CH), 76.75 (CH), 57.19 (CH), 48.63 (CH_2), 47.66 (CH), 23.33 (2 × CH_3), 21.28 (CH_3), 14.88 (CH_3), 13.61 (CH_3).

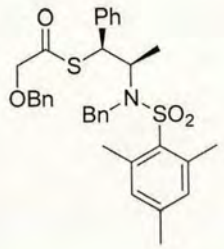
6.3 EXPERIMENTAL PROCEDURES FOR CHAPTER 3

(1'*S*,2'*R*)- 2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl-2-methoxy-thiolacetate 163



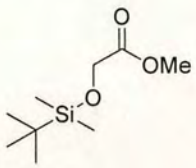
To a stirred solution of thiol **117** (5.0 g, 13 mmol), methoxyacetic acid (1.0 ml, 13 mmol) and DMAP (134 mg, 1.10 mmol) in CH_2Cl_2 (20 ml) was added EDCI (2.5 g, 14 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then at RT for 14 h. The solution was concentrated and the residue was dissolved in EtOAc (30 ml) and washed with NH_4Cl (2 × 20 ml, sat aq) and NaCl (2 × 20 ml, sat aq). The organics were combined and dried ($MgSO_4$) and the volatiles removed under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) gave **163** as a colourless solid (4.2 g, 71%); $\mathbf{R_f}$ (10% EtOAc in hexane) = 0.17; **mp** 76-77°C; $[\alpha]_D$ 60 (c 2.3, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1693 (C=O), 1603 (Ar), 1495 (Ar), 1152 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.44 (2H, d, *J* = 7.6 Hz, Ar*H*), 7.29-7.24 (3H, m, Ar*H*), 7.14 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.01 (2H, t, *J* = 7.2 Hz, Ar*H*), 6.82 (2H, s, Ar*H*), 6.70 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.83 (1H, d, *J* = 9.1 Hz, C*H*Ph), 4.78 (1H, d, $J_{A\text{-}B}$ = 16.2 Hz, CH_AH_BPh), 4.46 (1H, d, $J_{A\text{-}B}$ = 16.2 Hz, CH_AH_BPh), 4.17 (1H, dq, *J* = 9.1 and 6.8 Hz, C*H*CH_3), 3.99 (1H, d, $J_{C\text{-}D}$ = 16.1 Hz, CH_CH_DCO), 3.92 (1H, d, $J_{A\text{-}B}$ = 16.1 Hz, CH_CH_DCO), 3.37 (3H, s, OCH_3), 2.29 (3H, s, *p*-CH_3), 2.28 (6H, s, *o*-CH_3), 1.27 (3H, d, *J* = 6.8 Hz, CH_3CH); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 196.93 (C), 142.20 (C), 140.45 (2 × C), 139.81 (C), 138.35 (C), 132.63 (C), 132.01 (2 × CH), 128.61 (2 × CH), 128.26 (4 × CH), 127.51 (2 × CH), 127.29 (CH), 127.09 (CH), 77.04 (CH_2), 60.06 (CH_3), 56.35 (CH), 49.96 (CH), 47.29 (CH_2), 22.83 (2 × CH_3), 20.77 (CH_3), 17.29 (CH_3); ***m/z*** (FAB, THIOG) 588 ($[M+H]^+$, 9%), 406 (47), 316 (56), 207 (42), 183 (44), 169 (18), 119 (79), 91 (97), 79 (65), 77 (64); ***m/z*** (FAB, THIOG) 512 ($[M+H]^+$, 4%), 406 (21), 316 (43), 207 (16), 183 (30), 119 (61), 105 (48), 91 (74), 77 (46), 31 (14); **HRMS** (FAB, 3-NOBA) $[M+H]^+$ found 512.1926, $C_{28}H_{34}NO_4S_2$ requires 512.1929.

(1'*S*,2'*R*)-2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl-2-benzyloxy-thiolacetate 166



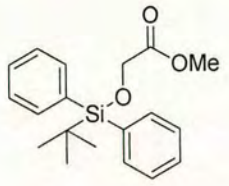
To a stirred solution of thiol **117** (6.0 g, 14 mmol), benzyloxyacetic acid (2.6 ml, 17 mmol) and DMAP (171 mg, 1.40 mmol) in CH_2Cl_2 (30 ml) was added DIC (2.7 ml, 17 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h (a bright yellow colour appeared) and then at RT for 14 h. The diisopropylurea formed was removed by filtration and the filtrate was concentrated. NaCl (40 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 ml) and washed with NaCl (20 ml, sat aq), HCl (20 ml, 1 N aq), NaCl (20 ml, sat aq), $NaHCO_3$ (20 ml, sat aq) and NaCl (20 ml, sat aq). The organics were dried ($MgSO_4$) and the volatiles removed under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) gave **166** as a waxy solid (5.6 g, 69%); $\mathbf{R_f}$ (10% EtOAc in hexane) = 0.23; $\mathbf{[\alpha]_D}$ 40.7 (c 5.50, $CHCl_3$); $\mathbf{\nu_{max}}$ (neat)/cm^{-1} 1691 (C=O), 1603 (Ar), 1495 (Ar), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.40 (2H, d, J = 7.6 Hz, Ar*H*), 7.28-7.24 (8H, m, Ar*H*), 7.10 (1H, t, J = 7.4 Hz, Ar*H*), 7.00 (2H, t, J = 7.1 Hz, Ar*H*), 6.78 (2H, s, Ar*H*), 6.68 (2H, d, J = 7.0 Hz, Ar*H*), 4.81 (1H, d, J = 9.2 Hz, C*H*Ph), 4.75 (1H, d, $J_{A\text{-}B}$ = 16.2 Hz, CH_AH_BPh), 4.49 (2H, s, OCH_2Ph), 4.42 (1H, d, $J_{A\text{-}B}$ = 16.2 Hz, CH_AH_BPh), 4.15 (1H, dq, J = 9.2 and 6.8 Hz, C*H*CH_3), 4.02 (1H, d, $J_{C\text{-}D}$ = 16.1 Hz, CH_CH_DCO), 3.95 (1H, d, $J_{A\text{-}B}$ = 16.1 Hz, CH_CH_DCO), 2.25 (9H, s, *o*-CH_3 and *p*-CH_3), 1.22 (3H, d, J = 6.8 Hz, CH_3CH); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 197.00 (C), 142.18 (C), 140.44 (2 × C), 139.84 (C), 138.36 (C), 136.47 (C), 132.66 (C), 132.01 (2 × CH), 128.60 (2 × CH), 128.39 (2 × CH), 128.29 (2 × CH), 128.25 (CH), 128.01 (2 × CH), 127.70 (2 × CH), 127.54 (2 × CH), 127.28 (CH), 127.09 (CH), 74.43 (CH_2), 73.85 (CH_2), 56.38 (CH), 50.06 (CH), 47.30 (CH_2), 22.75 (2 × CH_3), 20.77 (CH_3), 17.31 (CH_3); ***m/z*** (FAB, THIOG) 610 ($[M+Na]^+$, 6%), 406 (47), 316 (56), 207 (42), 183 (44), 169 (18), 119 (79), 91 (97), 79 (65), 77 (64); **HRMS** (FAB, 3-NOBA) $[M+H]^+$ found 588.2262, $C_{34}H_{38}NO_4S_2$ requires 588.2242.

Methyl 2-(*tert*-butyldimethylsilyloxy)acetate 191



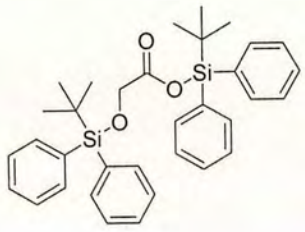
To a stirred solution of methyl glycolate (2.4 g, 26 mmol) in DMF (25 ml) was added imidazole (4.5 g, 65 mmol) and *tert*-butyl-dimethylsilyl chloride (4.8 g, 31 mmol) at 0 °C. The reaction mixture was stirred at RT for 4 h. NaCl (30 ml, sat aq) was added and the mixture was extracted with Et_2O (3 × 20 ml) and washed with NaCl (20 ml, sat aq). The organics were dried ($MgSO_4$) and the volatiles removed under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) gave **191** as a colourless oil (5.41 g, 100%); $\mathbf{R_f}$ (10% EtOAc in hexane) = 0.44; $\boldsymbol{\nu_{max}}$ (neat)/cm^{-1} 1764 (CO), 1256 ($SiCH_3$), 1006 (SiO), 838 ($SiCH_3$); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 4.13 (2H, s, CH_2CO), 3.61 (3H, s, OCH_3), 0.81 (9H, s, 3 × CH_3), 0.00 (6H, s, 2 × CH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 171.63 (C), 61.29 (CH_2), 51.21 (CH_3), 25.40 (3 × CH_3), 18.04 (C), – 5.83 (2 × CH_3); ***m/z*** (FAB, THIOG) 205 ($[M+H]^+$, 58%), 189 (28), 147 (63), 131 (23), 119 (32), 101 (12), 89 (100); **HRMS** (FAB, 3-NOBA) $[M+H]^+$ found 205.1254, $C_9H_{21}O_3Si$ requires 205.1260.

Methyl 2-(*tert*-butyldiphenylsilyloxy)acetate 192



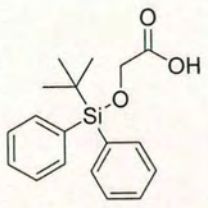
To a stirred solution of methyl glycolate (1.2 g, 13 mmol) in DMF (15 ml) was added imidazole (2.3 g, 33 mmol) and *tert*-butyl-diphenylsilyl chloride (4.2 ml, 16 mmol) at 0 °C. The reaction mixture was stirred at RT for 4 h. NaCl (20 ml, sat aq) was added and the mixture was extracted with Et_2O (3 × 20 ml) and washed with NaCl (20 ml, sat aq). The organics were dried ($MgSO_4$) and the volatiles removed under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) gave **192** as a colourless oil (4.31 g, 98%); $\mathbf{R_f}$ (10% EtOAc in hexane) = 0.41; ν_{max} (neat)/cm^{-1} 1763 (CO), 1589 (Ar), 1472 (Ar); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.64-7.54 (4H, m, Ar*H*), 7.29-7.19 (6H, m, Ar*H*), 4.13 (2H, s, CH_2CO), 3.49 (3H, s, OCH_3), 0.98 (9H, s, 3 × CH_3); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 171.15 (C), 135.27 (4 × CH), 132.50 (2 × C), 129.62 (2 × CH), 127.51 (4 × CH), 61.80 (CH_2), 51.18 (CH_3), 26.40 (3 × CH_3), 18.96 (C); **HRMS** (Electrospray, polyethylenimine) $[M+NH_4]^+$ found 346.1835, $C_{19}H_{28}NO_3Si$ requires 346.1833.

***Tert*-butyldiphenylsilyl 2-(*tert*-butyldiphenylsilyloxy)acetate 193**



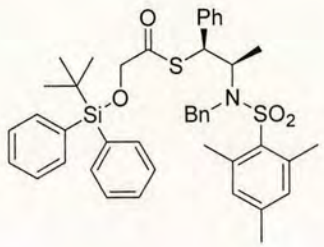
To a stirred solution of glycolic acid (550 mg, 7.23 mmol) in pyridine (20 ml) was added *tert*-butyl-diphenylsilyl chloride (7.7 ml, 29 mmol). The reaction mixture was stirred at RT for 3.5 h. NaCl (20 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 ml) and washed with HCl (3 × 20 ml, 1 N aq) and NaCl (20 ml, sat aq). The organics were dried ($MgSO_4$) and the volatiles removed under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) gave **193** as a colourless oil (3.81 g, 95%) which was shown to be unstable and was used immediately in the following reaction; $\mathbf{R_f}$ (10% EtOAc in hexane) = 0.55; $\mathbf{\nu_{max}}$ (neat)/cm^{-1} 1754 (CO), 1590 (Ar); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.61 (4H, d, *J* = 7.7 Hz, Ar*H*), 7.53 (4H, d, *J* = 7.7 Hz, Ar*H*), 7.34-7.15 (12H, m, Ar*H*), 4.28 (2H, s, OCH_2CO), 0.97 (9H, s, $C(CH_3)_3$), 0.96 (9H, s, $C(CH_3)_3$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 169.85 (C), 135.39 (4 × CH), 135.13 (4 × CH), 132.68 (2 × C), 131.52 (2 × C), 129.93 (2 × CH), 129.72 (2 × CH), 127.67 (4 × CH), 127.57 (4 × CH), 62.79 (CH_2), 26.73 (3 × CH_3), 26.52 (3 × CH_3), 19.03 (2 × C).

2-(*Tert*-butyldiphenylsilyloxy)acetic acid 194



To a stirred solution of silylester **193** (3.63 g, 6.58 mmol) in THF (2 ml) and MeOH (4 ml) was added a solution of K_2CO_3 (2.8 g, 20 mmol) in H_2O (2 ml) at RT. After stirring at RT for 30 min, the mixture was acidified to pH 3 using HCl (1 N aq) and the solution was extracted with Et_2O (3 × 10 ml). The organics were washed with NaCl (2 × 10 ml, sat aq), and dried ($MgSO_4$), and the volatiles removed under reduced pressure to give a colourless oil which was purified by flash chromatography (20% EtOAc in hexane-1% AcOH) to give the acid **194** as a colourless oil (1.78 g, 86%) which was shown to be unstable and was used immediately in the following reaction; $\mathbf{R_f}$ (20% EtOAc in hexane) = 0.23; $\boldsymbol{\nu_{max}}$ (neat)/cm^{-1} 3137 (br, OH), 1731 (C=O), 1590 (Ar); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 10.90 (1H, br, O*H*), 7.55 (4H, d, *J* = 7.3 Hz, Ar*H*), 7.32-7.17 (6H, m, Ar*H*), 4.14 (2H, s, OCH_2CO), 0.97 (6H, s, C(CH_3)$_3$); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 176.20 (C), 135.33 (4 × CH), 131.55 (2 × C), 129.43 (2 × CH), 127.51 (4 × CH), 61.64 (CH_2), 26.51 (3 × CH_3), 19.04 (C).

(1'*S*,2'*R*)-2-(*Tert*-butyldiphenylsilyloxy)-2'-(*N*-benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl thiolacetate 189



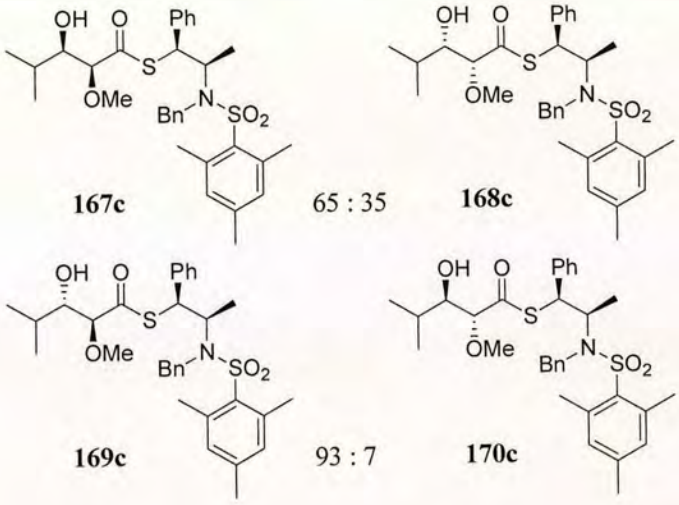
To a stirred solution of fresh prepared TBDPS-protected glycolic acid **194** (1.70 g, 5.41 mmol) in CH_2Cl_2 (5 ml) was added a solution of thiol **117** (1.01 g, 2.30 mmol) in CH_2Cl_2 (5 ml), then DMAP (28 mg, 0.23 mmol) and DIC (0.73 ml, 4.6 mmol). The reaction mixture was stirred at RT for 14 h. The diisopropylurea formed was removed by filtration and the filtrate was concentrated. NaCl (20 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 ml) and washed with NaCl (10 ml, sat aq), HCl (10 ml, 1N aq), NaCl (10 ml, sat aq), $NaHCO_3$ (10 ml, sat aq) and NaCl (10 ml, sat aq). The organics were dried ($MgSO_4$) and the volatiles removed under reduced pressure. Purification by flash chromatography (10% EtOAc in hexane) gave **189** as a waxy solid (1.65 g, 98%); $\mathbf{R_f}$ (10% EtOAc in hexane) = 0.35; $[\alpha]_D$ 40.0 (c 4.40, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1694 (C=O), 1603 (Ar), 1495 (Ar); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.61-7.55 (4H, m, Ar*H*), 7.43-7.24 (11H, m, Ar*H*), 7.15 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.04 (2H, t, *J* = 7.6 Hz, Ar*H*), 6.84 (2H, s, Ar*H*), 6.75 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.84 (1H, d, $J_{A\text{-}B}$ = 16.3 Hz, CH_AH$_B$Ph), 4.80 (1H, d, *J* = 8.7 Hz, C*H*Ph), 4.50 (1H, d, $J_{A\text{-}B}$ = 16.3 Hz, CH$_A$$H_B$Ph), 4.21 (1H, dq, *J* = 8.7 & 6.8 Hz, C*H*CH$_3$), 4.15 (2H, d, *J* = 1.5 Hz, CH_2 CO), 2.32 (6H, s, *o*-CH_3), 2.30 (3H, s, *p*-CH_3), 1.24 (3H, d, *J* = 6.8 Hz, CH_3CH) 1.08 (9H, s, (CH_3)$_3$C); **^{13}C NMR** δ (62.9 MHz, $CDCl_3$) 198.95 (C), 142.19 (C), 140.44 (2 × C), 140.21 (C), 138.48 (C), 135.35 (4 × C), 134.67 (C), 132.89 (C), 132.04 (3 × CH), 129.94 (CH), 128.53 (3 × CH), 128.23 (3 × CH), 127.78 (C), 127.73 (3 × CH), 127.61 (3 × CH), 127.22 (CH), 127.01 (CH), 69.10 (CH_2), 56.52 (CH), 50.08 (CH), 47.45 (CH_2), 26.53 (3 × CH_3), 23.47 (2 × CH_3), 20.80 (CH_3), 19.09 (C), 17.31 (CH_3); **HRMS** (ESI, +) $[M+H]^+$ found 736.2955, $C_{43}H_{50}NO_4S_2Si$ requires 736.2945.

General procedure D: Synthesis of Me-Protected *Syn* Glycolate Aldol Adducts

To a stirred solution of thiolpropionate ester **163** (150 mg, 0.294 mmol) in CH_2Cl_2 (10 ml) at - 78 °C was added the boron triflate (1.0 M in hexane, 0.88 mmol) then amine base (0.74 mmol). The reaction mixture was stirred at - 78 °C for 2 h, then aldehyde was added (0.88 mmol). The reaction was stirred at - 78 °C for 2 h and then at 0 °C for 1 h. The mixture was quenched by the addition of pH 7 buffer and methanol (1:1, 4 ml) and diluted with methanol (4 ml) to make a homogeneous solution. After careful addition of H_2O_2 (30% aq, 2 ml) the mixture was stirred at RT for 1 h.

NaCl (20 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The combined organics were washed with $NaHCO_3$ (10 ml, sat aq) and NaCl (10 ml, sat aq), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldol product. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers that was separated by **HPLC**.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-hydroxy-2-methoxy-4-methyl-thiolpentanoate 167c



167c 65 : 35 **168c**

169c 93 : 7 **170c**

General procedure D was followed with thiolpropionate ester **163** (300 mg, 0.588 mmol), dicyclohexylboron triflate (1.0 M in hexane, 1.8 ml, 1.8 mmol), triethylamine (206 µl, 1.48 mmol) and isobutyraldehyde (162 µl, 1.76 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **167c**, **168c**, **169c** and **170c** that was separated by **HPLC** (228 mg, 67%) (ds $_{anti\ :\ anti}$ = 93 : 7, ds $_{syn\ :\ anti}$ = 98 : 2, ds $_{syn\ :\ syn}$ = 65 : 35).

(2*S*,3*R*)-Major *syn* diastereoisomer 167c: HPLC R_t (10% EtOAc in hexane, flow rate: 10 ml/min) = 54 min; **R_f** (20% EtOAc in hexane) = 0.32; **$[\alpha]_D$** = + 127 (c 0.45, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3519 (OH), 1685 (C=O), 1603 (Ar), 1495 (Ar), 1322 (SO_2N), 1152 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.40 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.31-7.21 (3H, m, Ar*H*), 7.20 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.01 (2H, t, *J* = 7.1 Hz, Ar*H*), 6.81 (2H, s, Ar*H*), 6.68 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.78 (1H, d, *J* = 9.1 Hz, C*H*Ph), 4.74 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.48 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.18 (1H, dq, *J* = 9.1 & 6.8 Hz, C*H*CH_3), 3.70 (1H, d, *J* = 3.3 Hz, C*H*OCH_3), 3.46 (1H, dd, *J* = 7.2 & 3.3 Hz, C*H*OH), 3.37 (3H, s, OCH_3), 2.29 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 1.84-1.68 (2H, br m, O*H* & C*H*$(CH_3)_2$), 1.28 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.98 (3H, d, *J* = 6.7 Hz, CH(CH_3)$_A$$(CH_3)_B$), 0.90 (3H, d, *J* = 6.7 Hz, CH$(CH_3)_A$(CH_3)$_B$); **^{13}C NMR** δ (90.5 MHz, CDCl3) 200.21 (C), 142.00 (C), 140.29 (2 × C), 139.66 (C), 138.14 (C), 132.46 (C), 131.79 (2 × CH), 128.40 (2 × CH), 128.05 (4 × CH), 127.40 (2 × CH), 127.04 (CH),

126.84 (CH), 87.20 (CH), 77.68 (CH), 59.95 (CH_3), 56.55 (CH), 50.17 (CH), 46.97 (CH_2), 30.39 (CH), 22.59 (2 × CH_3), 20.60 (CH_3), 19.10 (CH_3), 17.66 (CH_3), 16.84 (CH_3); ***m/z*** (FAB, THIOG) 584 ($[M+H]^+$, 13%), 402 (21), 316 (34), 295 (27), 119 (30), 91 (100); **HRMS** (FAB, THIOG) $[M+H]^+$ found 584.2489, $C_{32}H_{42}NO_5S_2$ requires 584.2504.

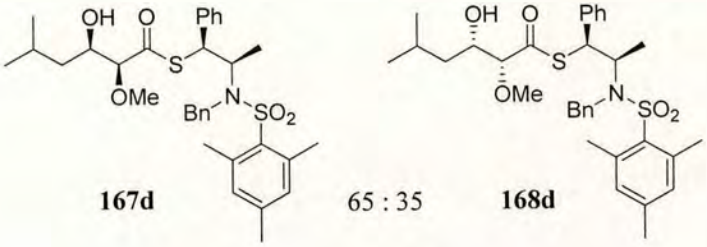
(2*R*,3*S*)-Minor *syn* diastereoisomer 168c: HPLC R_t (10% EtOAc in hexane, flow rate: 10 ml/min) = 65 min; **R_f** (20% EtOAc in hexane) = 0.27; **$[\alpha]_D$** = - 8.0 (c 0.25, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3530 (OH), 1685 (C=O), 1603 (Ar), 1495 (Ar), 1321 (SO_2N), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.41 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.31-7.21 (3H, m, Ar*H*), 7.11 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.02 (2H, t, *J* = 7.6 Hz, Ar*H*), 6.81 (2H, s, Ar*H*), 6.71 (2H, d, *J* = 7.0 Hz, Ar*H*), 4.81 (1H, d, *J* = 16.3 Hz, C$H_A$$H_B$Ph), 4.81 (1H, d, *J* = 9.1 Hz, C*H*Ph), 4.46 (1H, d, *J* = 16.3 Hz, CH$_A$$H_B$Ph), 4.18 (1H, dq, *J* = 9.1 & 6.8 Hz, C*H*CH_3), 3.69 (1H, d, *J* = 4.0 Hz, C*H*OCH_3), 3.43 (3H, s, OCH_3), 3.34 (1H, dd, *J* = 6.3 & 4.0 Hz, C*H*OH), 2.29 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 1.64-1.48 (2H, br m, O*H* & C*H*$(CH_3)_2$), 1.26 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.88 (3H, d, *J* = 6.7 Hz, CH(CH_3)$_A$$(CH_3)_B$), 0.82 (3H, d, *J* = 6.7 Hz, CH$(CH_3)_A$(CH_3)$_B$).

(2*S*,3*S*)-Major *anti* diastereoisomer 169c: HPLC R_t (10% EtOAc in hexane, flow rate: 10 ml/min) = 60 min; **R_f** (20% EtOAc in hexane) = 0.29; **$[\alpha]_D$** = - 1.7 (c 0.60, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3523 (OH), 1685 (C=O), 1603 (Ar), 1495 (Ar), 1321 (SO_2N), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.43 (2H, d, *J* = 7.6 Hz, Ar*H*), 7.32-7.23 (3H, m, Ar*H*), 7.11 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.00 (2H, t, *J* = 7.2 Hz, Ar*H*), 6.81 (2H, s, Ar*H*), 6.71 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.81 (1H, d, *J* = 16.3 Hz, C$H_A$$H_B$Ph), 4.81 (1H, d, *J* = 9.1 Hz, C*H*Ph), 4.46 (1H, d, *J* = 16.3 Hz, CH$_A$$H_B$Ph), 4.18 (1H, dq, *J* = 9.1 & 6.8 Hz, C*H*CH_3), 3.62 (1H, d, *J* = 6.6 Hz, C*H*OCH_3), 3.43-3.37 (1H, m, C*H*OH), 3.40 (3H, s, OCH_3), 2.28 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 1.78-1.65 (1H, m, C*H*$(CH_3)_2$), 1.64-1.48 (1H, br, O*H*), 1.27 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.84 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_A$$(CH_3)_B$), 0.82 (3H, d, *J* = 6.7 Hz, CH$(CH_3)_A$(CH_3)$_B$); **^{13}C NMR** δ (90.5 MHz, CDCl3) 200.08 (C), 142.23 (C), 140.44 (2 × C), 139.68 (C), 138.38 (C), 132.71 (C), 132.04 (2 × CH), 128.53 (2 × CH), 128.29 (4 × CH), 127.51 (2 × CH), 127.30 (CH), 127.10 (CH), 87.98 (CH), 76.36 (CH), 59.75 (CH_3), 56.39 (CH), 50.50 (CH), 47.44 (CH_2), 29.03 (CH), 22.78 (2 × CH_3), 20.80 (CH_3), 19.34 (CH_3), 17.42 (CH_3), 16.08 (CH_3); ***m/z*** (FAB, THIOG) 584 ($[M+H]^+$, 22%), 406 (29), 316 (56), 295 (50), 183 (31),

119 (74), 91 (100); **HRMS** (FAB, THIOG) $[M+H]^+$ found 584.2511, $C_{32}H_{42}NO_5S_2$ requires 584.2504.

(2*R*,3*R*)-Minor *anti* diastereoisomer 170c: HPLC R_t (10% EtOAc in hexane, flow rate: 10 ml/min) = 53 min; **R_f** (20% EtOAc in hexane) = 0.32; **$[\alpha]_D$** = + 20 (c 0.25, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3521 (OH), 1684 (C=O), 1603 (Ar), 1495 (Ar), 1321 (SO_2N), 1153 (SO_2N); **^1H NMR** δ (250 MHz, $CDCl_3$) 7.40 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.31-7.18 (3H, m, Ar*H*), 7.13 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.01 (2H, t, *J* = 7.7 Hz, Ar*H*), 6.81 (2H, s, Ar*H*), 6.73 (2H, d, *J* = 7.2 Hz, Ar*H*), 4.80 (1H, d, *J* = 8.6 Hz, C*H*Ph), 4.76 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.48 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.21 (1H, dq, *J* = 8.6 & 6.8 Hz, C*H*CH_3), 3.63 (1H, d, *J* = 6.1 Hz, C*H*OCH_3), 3.51 (1H, dd, *J* = 6.1 Hz, C*H*OH), 3.33 (3H, s, OCH_3), 2.30 (6H, s, 2 × *o*-CH_3), 2.29 (3H, s, *p*-CH_3), 1.91-1.78 (1H, m, C*H*$(CH_3)_2$), 1.26 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.94 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_A(CH_3)_B$), 0.90 (3H, d, *J* = 6.7 Hz, $CH(CH_3)_A(CH_3)_B$).

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-hydroxy-2-methoxy-5-methyl-thiolhexanoate 167d



167d 65 : 35 **168d**

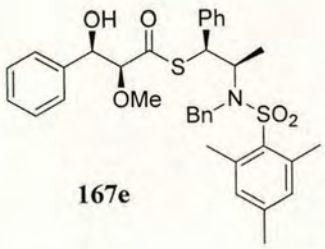
General procedure D was followed with thiolpropionate ester **163** (150 mg, 0.294 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.88 ml, 0.88 mmol), triethylamine (103 μl, 0.74 mmol) and isovaleraldehyde (97 μl, 0.88 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **167d** and **168d** that was separated by **HPLC** (154 mg, 88%) (ds $_{syn\,:\,syn}$ = 65 : 35, ds $_{syn\,:\,anti}$ = 98 : 2).

(2*S*,3*R*)-Major *syn* diastereoisomer 167d: HPLC R_t (20% EtOAc in hexane, flow rate: 10 ml/min) = 21 min; **R_f** (20% EtOAc in hexane) = 0.26; **$[\alpha]_D$** = + 4.31 (c 3.25, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3520 (OH), 1684 (C=O), 1603 (Ar), 1495 (Ar), 1322 (SO_2N), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.42 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.31-7.22 (3H, m, Ar*H*), 7.10 (1H, t, *J* = 7.4 Hz, Ar*H*), 6.97 (2H, t, *J* = 7.7 Hz, Ar*H*), 6.80 (2H, s, Ar*H*), 6.70 (2H, d, *J* = 7.0 Hz, Ar*H*), 4.80 (1H, d, *J* = 16.3 Hz, CH_AH$_B$Ph), 4.78 (1H, d, *J* = 9.0 Hz, C*H*Ph), 4.44 (1H, d, *J* = 16.3 Hz, CH$_A$$H_B$Ph), 4.16 (1H, dq, *J* = 9.0 & 6.8 Hz, C*H*CH$_3$), 3.70-3.58 (1H, m, C*H*OH), 3.46 (1H, d, *J* = 5.1 Hz, C*H*OCH$_3$), 3.40 (3H, s, OCH_3), 2.28 (6H, s, 2 × *o*-CH_3), 2.27 (3H, s, *p*-CH_3), 2.07 (1H, br d, *J* = 5.6 Hz, O*H*), 1.66-1.52 (1H, m, C*H*CH$_2$), 1.27-1.15 (1H, m, CH_CH$_D$), 1.25 (3H, d, *J* = 6.8 Hz, CHCH_3), 0.95-0.80 (1H, m, CH$_C$$H_D$), 0.76 (3H, d, *J* = 6.6 Hz, CH(CH_3)(CH$_3$)), 0.66 (3H, d, *J* = 6.6 Hz, CH(CH$_3$)(CH_3)); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 199.21 (C), 142.21 (C), 140.40 (2 × C), 139.74 (C), 138.35 (C), 132.68 (C), 132.01 (2 × CH), 128.45 (2 × CH), 128.26 (2 × CH), 128.22 (2 × CH), 127.44 (2 × CH), 127.27 (CH), 127.07 (CH), 90.19 (CH), 70.59 (CH), 59.80 (CH_3), 56.14 (CH), 50.59 (CH), 47.44 (CH_2), 40.93 (CH_2), 24.02 (CH), 23.22 (CH_3), 22.73 (2 × CH_3), 21.22 (CH_3), 20.77 (CH_3), 17.48 (CH_3); ***m/z*** (FAB, THIOG) 598 ([M+H]$^+$, 30%), 416 (41), 316 (49), 309

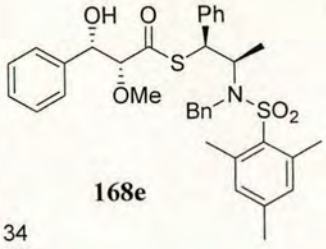
(47), 119 (65), 91 (100); **HRMS** (FAB, THIOG) $[M+H]^+$ found 598.2641, $C_{33}H_{44}NO_5S_2$ requires 598.2660.

(2*R*,3*S*)-Minor *syn* diastereoisomer 168d: HPLC R_t (20% EtOAc in hexane, flow rate: 10 ml/min) = 19 min; **R_f** (20% EtOAc in hexane) = 0.30; **$[\alpha]_D$** = + 83.2 (c 2.20, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3520 (OH), 1684 (C=O), 1603 (Ar), 1495 (Ar), 1322 (SO_2N), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.40 (2H, d, *J* = 7.9 Hz, Ar*H*), 7.30-7.20 (3H, m, Ar*H*), 7.13 (1H, t, *J* = 7.0 Hz, Ar*H*), 7.01 (2H, t, *J* = 7.1 Hz, Ar*H*), 6.80 (2H, s, Ar*H*), 6.67 (2H, d, *J* = 7.0 Hz, Ar*H*), 4.79 (1H, d, *J* = 9.2 Hz, C*H*Ph), 4.75 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.45 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.19 (1H, dq, *J* = 9.2 & 6.8 Hz, C*H*CH_3), 3.87-3.75 (1H, m, C*H*OH), 3.48 (1H, d, *J* = 4.3 Hz, C*H*OCH_3), 3.35 (3H, s, OCH_3), 2.27 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 2.12 (1H, br d, *J* = 7.1 Hz, O*H*), 1.80-1.67 (1H, m, C*H*CH_2), 1.40 (1H, ddd, *J* = 13.8, 9.8 & 5.0 Hz, CH_CH_D), 1.27 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.16 (1H, ddd, *J* = 13.8, 8.8 & 3.4 Hz, CH_CH_D), 0.89 (3H, d, *J* = 6.6 Hz, CH(CH_3)(CH_3)), 0.83 (3H, d, *J* = 6.6 Hz, CH(CH_3)(CH_3)); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 199.87 (C), 142.20 (C), 140.47 (2 × C), 139.83 (C), 138.27 (C), 132.68 (C), 131.99 (2 × CH), 128.63 (2 × CH), 128.27 (2 × CH), 128.22 (2 × CH), 127.59 (2 × CH), 127.27 (CH), 127.07 (CH), 89.85 (CH), 70.76 (CH), 60.15 (CH_3), 56.61 (CH), 50.25 (CH), 47.23 (CH_2), 41.66 (CH_2), 24.26 (CH), 23.31 (CH_3), 22.76 (2 × CH_3), 21.53 (CH_3), 20.79 (CH_3), 17.21 (CH_3).

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-hydroxy-2-methoxy-3-phenyl thiopropionate 167e



167e



168e

66 : 34
68 : 32
26 : 74
31 : 69
21 : 79
47 : 53

Method A: General procedure D was followed with thiolpropionate ester **163** (150 mg, 0.294 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.88 ml, 0.88 mmol), triethylamine (103 μl, 0.74 mmol) and benzaldehyde (94 μl, 0.88 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **167e** and **168e** that was separated by **HPLC** (163 mg, 90%) (ds $_{syn\,:\,syn}$ = 66 : 34, ds $_{syn\,:\,anti}$ = 91 : 9, ds $_{anti\,:\,anti}$ = 99 : 1).

(2*S*,3*R*)-Major *syn* diastereoisomer 167e: HPLC R_t (20% EtOAc in hexane, flow rate:10 ml/min) = 29 min; **R_f** (20% EtOAc in hexane) = 0.23; **$[\alpha]_D$** = + 21.1 (c 2.85, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3500 (OH), 1687 (C=O), 1603 (Ar), 1495 (Ar), 1321 (SO_2N), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.44-7.35 (2H, m, Ar*H*), 7.31-7.10 (7H, m, Ar*H*), 7.08-6.97 (4H, m Ar*H*), 6.84 (2H, s, Ar*H*), 6.67 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.77 (1H, d, *J* = 16.2 Hz, CH_AH$_B$Ph), 4.77-4.69 (1H, m, C*H*OH), 4.74 (1H, d, *J* = 9.2 Hz, C*H*Ph), 4.39 (1H, d, *J* = 16.2 Hz, CH$_A$$H_B$Ph), 4.14 (1H, dq, *J* = 9.2 & 6.8 Hz, C*H*CH_3), 3.74 (1H, d, *J* = 5.5 Hz, C*H*OCH_3), 3.32 (3H, s, OCH_3), 2.80 (1H, br d, *J* = 3.9 Hz, O*H*), 2.30 (3H, s, *p*-CH_3), 2.28 (6H, s, 2 × *o*-CH_3), 1.18 (3H, d, *J* = 6.8 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 197.65 (C), 142.20 (C), 140.40 (2 × C), 139.63 (C), 138.30 (C), 138.18 (C), 132.60 (C), 132.00 (2 × CH), 128.51 (2 × CH), 128.24 (4 × CH), 128.13 (2 × CH), 127.98 (CH), 127.51 (2 × CH), 127.25 (CH), 127.07 (CH), 126.32 (2 × CH), 90.99 (CH), 74.49 (CH), 59.79 (CH_3), 56.06 (CH), 50.64 (CH), 47.30 (CH_2), 22.71 (2 × CH_3), 20.76 (CH_3), 17.43 (CH_3); ***m/z*** (FAB, THIOG) 618 ($[M+H]^+$, 12%), 406 (39), 316 (56), 183 (55), 151 (47), 119 (92), 91 (100); **HRMS** (FAB, GLYCEROL) $[M+H]^+$ found 618.2343, $C_{35}H_{40}NO_5S_2$ requires 618.2347.

(2*R*,3*S*)-Minor *syn* diastereoisomer 168e: HPLC R_t (20% EtOAc in hexane, flow rate: 10 ml/min) = 25 min; **R_f** (20% EtOAc in hexane) = 0.26; **$[\alpha]_D$** = + 95 (c 2.8, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3500 (OH), 1685 (C=O), 1603 (Ar), 1495 (Ar), 1321 (SO_2N), 1152 (SO_2N); **^1H NMR** δ (250 MHz, $CDCl_3$) 7.42-7.35 (2H, m, Ar*H*), 7.30-7.20 (8H, m, Ar*H*), 7.16-7.07 (1H, m Ar*H*), 6.98 (2H, t, *J* = 7.7 Hz, Ar*H*), 6.79 (2H, s, Ar*H*), 6.61 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.91 (1H, br s, C*H*OH), 4.73 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.73 (1H, d, *J* = 9.2 Hz, C*H*Ph), 4.40 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.12 (1H, dq, *J* = 9.2 & 6.8 Hz, C*H*CH_3), 3.77 (1H, d, *J* = 3.9 Hz, C*H*OCH_3), 3.21 (3H, s, OCH_3), 2.80 (1H, br d, *J* = 5.6 Hz, O*H*), 2.27 (3H, s, *p*-CH_3), 2.25 (6H, s, 2 × *o*-CH_3), 1.30 (3H, d, *J* = 6.8 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 198.86 (C), 142.18 (C), 140.47 (2 × C), 139.73 (C), 139.11 (C), 138.29 (C), 132.67 (C), 131.98 (2 × CH), 128.65 (2 × CH), 128.23 (6 × CH), 127.91 (CH), 127.54 (2 × CH), 127.26 (CH), 127.05 (CH), 126.14 (2 × CH), 90.37 (CH), 74.22 (CH), 60.34 (CH_3), 56.47 (CH), 50.39 (CH), 47.19 (CH_2), 22.74 (2 × CH_3), 20.77 (CH_3), 17.26 (CH_3).

Method B: General procedure D was followed with thiolpropionate ester **163** (150 mg, 0.294 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.88 ml, 0.88 mmol) and diisopropylethylamine (0.13 ml, 0.74 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (94 µl, 0.88 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **167e** and **168e** that was separated by **HPLC** (154 mg, 85%) (ds $_{syn\,:\,syn}$ = 68 : 32, ds $_{syn\,:\,anti}$ = 95 : 5, ds $_{anti\,:\,anti}$ = 99 : 1).

Method C: General procedure D was followed with thiolpropionate ester **163** (150 mg, 0.294 mmol), dibutylboron triflate (1.0 M in hexane, 0.88 ml, 0.88 mmol) and triethylamine (104 µl, 0.74 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (94 µl, 0.88 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **167e** and **168e** that was separated by **HPLC** (152 mg, 84%) (ds $_{syn\,:\,syn}$ = 26 : 74, ds $_{syn\,:\,anti}$ = 91 : 9, ds $_{anti\,:\,anti}$ = 62 : 38).

Method D: General procedure D was followed with thiolpropionate ester **163** (150 mg, 0.294 mmol), dibutylboron triflate (1.0 M in hexane, 0.88 ml, 0.88 mmol) and diisopropylethylamine (0.13 ml, 0.74 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (94 µl, 0.88 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **167e** and **168e** that was separated by **HPLC** (141 mg, 78%) (ds $_{syn\,:\,syn}$ = 31 : 69, ds $_{syn\,:\,anti}$ = 98 : 2, ds $_{anti\,:\,anti}$ = 49 : 51).

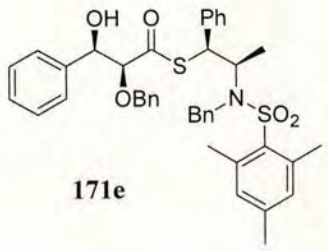
Method E: General procedure D was followed with thiolpropionate ester **163** (100 mg, 0.196 mmol), 9-BBN-triflate (0.5 M in hexane, 1.2 ml, 0.59 mmol) and triethylamine (69 µl, 0.49 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (63 µl, 0.59 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **167e** and **168e** that was separated by **HPLC** (88 mg, 73%) (ds $_{syn\,:\,syn}$ = 21 : 79, ds $_{syn\,:\,anti}$ = 99 : 1).

Method F: General procedure D was followed with thiolpropionate ester **163** (100 mg, 0.196 mmol), 9-BBN-triflate (0.5 M in hexane, 1.2 ml, 0.59 mmol) and diisopropylethylamine (86 µl, 0.49 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (63 µl, 0.59 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **167e** and **168e** that was separated by **HPLC** (96 mg, 80%) (ds $_{syn\,:\,syn}$ = 47 : 53, ds $_{syn\,:\,anti}$ = 96 : 4, ds $_{anti\,:\,anti}$ = 99 : 1).

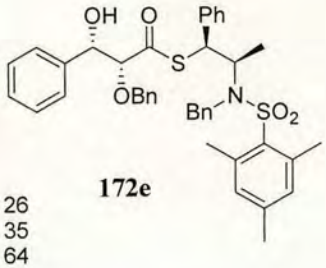
General procedure E: Synthesis of Bn-Protected *Syn* Glycolate Aldol Adducts

To a stirred solution of thiolpropionate ester **166** (150 mg, 0.256 mmol) in CH_2Cl_2 (10 ml) at - 78 °C was added the boron triflate (1.0 M in hexane, 0.77 mmol) then amine base (0.64 mmol). The reaction mixture was stirred at - 78 °C for 1 h, then benzaldehyde was added (82 µl, 0.77 mmol). The reaction was stirred at - 78 °C for 2 h and then at 0 °C for 1.5 h. The mixture was quenched by the addition of pH 7 buffer and methanol (1:1, 4 ml) and diluted with methanol (4 ml) to make a homogeneous solution. After careful addition of H_2O_2 (30% aq, 2 ml) the mixture was stirred at RT for 30 min. NaCl (10 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The combined organics were washed with $NaHCO_3$ (10 ml, sat aq) and NaCl (10 ml, sat aq), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldol product. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **171e** and **172e** that was separated by **HPLC**.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)- 2-benzoxy-3-hydroxy-3-phenyl thiopropionate 171e



171e



172e

74 : 26
65 : 35
36 : 64
28 : 72
31 : 69
43 : 57
55 : 45
42 : 58
62 : 38

Method A: General procedure E was followed with thiolpropionate ester **166** (150 mg, 0.256 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.77 ml, 0.77 mmol) and triethylamine (90 µl, 0.64 mmol). Benzaldehyde was added (82 µl, 0.77 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **171e** and **172e** that was separated by **HPLC** (159 mg, 90%) (ds $_{syn\,:\,syn}$ = 74 : 26, ds $_{syn\,:\,anti}$ = 99 : 1).

(2*S*,3*R*)-Major *syn* diastereoisomer 171e: HPLC R_t (20% EtOAc in hexane, flow rate:10 ml/min) = 20 min; **R_f** (20% EtOAc in hexane) = 0.28; **$[\alpha]_D$** = + 13.7 (c 6.50, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3512 (OH), 1690 (C=O), 1603 (Ar), 1494 (Ar), 1321 (SO_2N), 1152 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.42-7.33 (2H, m, Ar*H*), 7.28-7.20 (6H, m, Ar*H*), 7.20-7.10 (6H, m, Ar*H*), 7.05-6.96 (4H, m, Ar*H*), 6.80 (2H, s, Ar*H*), 6.68 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.80-4.70 (1H, br, C*H*OH), 4.77 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.75 (1H, d, *J* = 8.9 Hz, C*H*Ph), 4.51 (1H, d, *J* = 11.2 Hz, CH_CH_DPh), 4.40 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.26 (1H, d, *J* = 11.2 Hz, CH_CH_DPh), 4.15 (1H, dq, *J* = 8.9 & 6.8 Hz, C*H*CH_3), 3.94 (1H, d, *J* = 5.2 Hz, C*H*COS), 2.78 (1H, br d, *J* = 4.7 Hz, O*H*), 2.27 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 1.18 (3H, d, *J* = 6.8 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 197.77 (C), 142.17 (C), 140.33 (2 × C), 139.59 (C), 138.28 (2 × C), 135.89 (C), 132.61 (C), 131.97 (2 × CH), 128.42 (2 × CH), 128.30 (3 × CH), 128.20 (4 × CH), 128.06 (4 × CH), 127.84 (CH), 127.52 (2 × CH), 127.20 (CH), 127.04 (CH), 126.21 (2 × CH), 88.26 (CH), 74.49 (CH), 73.89 (CH_2), 56.07 (CH), 50.77 (CH), 47.33 (CH_2), 22.69 (2 × CH_3), 20.72 (CH_3), 17.42 (CH_3); ***m/z*** (FAB, THIOG) 716 ([M+Na]$^+$, 7%),

512 (22), 406 (36), 316 (49), 134 (25), 119 (60), 91 (100); **HRMS** (FAB, THIOG) $[M+H]^+$ found 694.2657, $C_{41}H_{44}NO_5S_2$ requires 694.2660.

(2*R*,3*S*)-Minor *syn* diastereoisomer 172e: HPLC R_t (20% EtOAc in hexane, flow rate: 10 ml/min) = 18 min; **R_f** (20% EtOAc in hexane) = 0.31; **$[\alpha]_D$** = + 48 (c 8.1, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3522 (OH), 1684 (C=O), 1603 (Ar), 1495 (Ar), 1319 (SO_2N), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.46-7.37 (2H, m, Ar*H*), 7.32-7.12 (12H, m, Ar*H*), 7.08-6.98 (4H, m, Ar*H*), 6.82 (2H, s, Ar*H*), 6.66 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.96 (1H, br s, C*H*OH), 4.79 (1H, d, *J* = 9.0 Hz, C*H*Ph), 4.77 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.48 (1H, d, *J* = 11.2 Hz, CH_CH_DPh), 4.44 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.17 (1H, d, *J* = 11.2 Hz, CH_CH_DPh), 4.15 (1H, dq, *J* = 9.0 & 6.8 Hz, C*H*CH_3), 3.99 (1H, d, *J* = 3.8 Hz, C*H*COS), 2.91 (1H, br, O*H*), 2.29 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 1.24 (3H, d, *J* = 6.8 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 198.93 (C), 142.13 (C), 140.40 (2 × C), 139.75 (C), 139.15 (C), 138.26 (C), 135.80 (C), 132.66 (C), 131.94 (2 × CH), 128.60 (2 × CH), 128.19 (3 × CH), 128.12 (4 × CH), 128.00 (4 × CH), 127.76 (CH), 127.52 (2 × CH), 127.21 (CH), 127.01 (CH), 126.05 (2 × CH), 87.62 (CH), 74.33 (CH), 74.23 (CH_2), 56.48 (CH), 50.51 (CH), 47.16 (CH_2), 22.71 (2 × CH_3), 20.73 (CH_3), 17.23 (CH_3).

Method B: General procedure E was followed with thiolpropionate ester **166** (150 mg, 0.256 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.77 ml, 0.77 mmol) and diisopropylethylamine (0.11 ml, 0.64 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (82 µl, 0.77 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **171e** and **172e** that was separated by **HPLC** (148 mg, 84%) ($ds_{syn\,:\,syn}$ = 65 : 35, $ds_{syn\,:\,anti}$ = 99 : 1).

Method C: General procedure E was followed with thiolpropionate ester **166** (150 mg, 0.256 mmol), dibutylboron triflate (1.0 M in hexane, 0.77 ml, 0.77 mmol) and triethylamine (90 µl, 0.64 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (82 µl, 0.77 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **171e** and **172e** that was separated by **HPLC** (156 mg, 82%) ($ds_{syn\,:\,syn}$ = 36 : 64, $ds_{syn\,:\,anti}$ = 99 : 1).

Method D: General procedure E was followed with thiolpropionate ester **166** (150 mg, 0.256 mmol), dibutylboron triflate (1.0 M in hexane, 0.77 ml, 0.77 mmol) and diisopropylethylamine (0.11 ml, 0.64 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (82 µl, 0.77 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **171e** and **172e** that was separated by **HPLC** (131 mg, 74%) (ds $_{syn\,:\,syn}$ = 28 : 72, ds $_{syn\,:\,anti}$ = 94 : 6).

Method E: General procedure E was followed with thiolpropionate ester **166** (100 mg, 0.170 mmol), 9-BBN-triflate (0.5 M in hexane, 1.0 ml, 0.51 mmol) and triethylamine (61 µl, 0.43 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (55 µl, 0.51 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **171e** and **172e** that was separated by **HPLC** (94 mg, 80%) (ds $_{syn\,:\,syn}$ = 31 : 69, ds $_{syn\,:\,anti}$ = 93 : 7).

Method F: General procedure E was followed with thiolpropionate ester **166** (100 mg, 0.170 mmol), 9-BBN-triflate (0.5 M in hexane, 1.0 ml, 0.51 mmol) and diisopropylethylamine (75 µl, 0.43 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (55 µl, 0.51 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 1.5 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **171e** and **172e** that was separated by **HPLC** (93 mg, 79%) (ds $_{syn\,:\,syn}$ = 43 : 57, ds $_{syn\,:\,anti}$ = 97 : 3).

Method G: General procedure E was followed with thiolpropionate ester **166** (150 mg, 0.256 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.77 ml, 0.77 mmol) and triethylamine (90 µl, 0.64 mmol). The reaction mixture was stirred at 0 °C for 1 h, then benzaldehyde was added (82 µl, 0.77 mmol). The reaction was stirred at 0 °C for 1 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **171e** and **172e** that was separated by **HPLC** (107 mg, 60%) (ds $_{syn\,:\,syn}$ = 55 : 45, ds $_{syn\,:\,anti}$ = 68 : 32).

Method H: General procedure E was followed with thiolpropionate ester **166** (150 mg, 0.256 mmol), dibutylboron triflate (1.0 M in hexane, 0.77 ml, 0.77 mmol) and diisopropylethylamine (0.11 ml, 0.64 mmol). The reaction mixture was stirred at 0 °C for 1 h, then benzaldehyde was added (82 µl, 0.77 mmol). The reaction was stirred at 0 °C for 2 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **171e** and **172e** that was separated by **HPLC** (120 mg, 68%) ($ds_{syn:syn}$ = 42 : 58, $ds_{syn:anti}$ = 93 : 7).

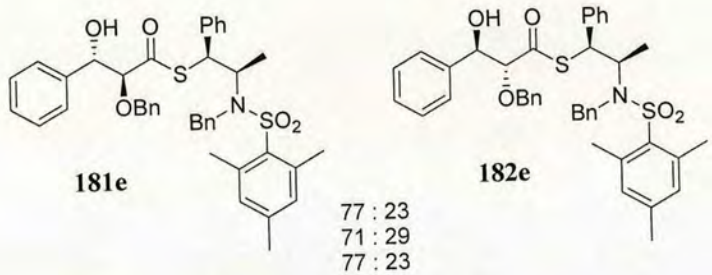
Method I: General procedure E was followed with thiolpropionate ester **166** (150 mg, 0.256 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.77 ml, 0.77 mmol) and triethylamine (90 µl, 0.64 mmol). The reaction mixture was stirred at RT for 1 h, then benzaldehyde was added (82 µl, 0.77 mmol). The reaction was stirred at RT for 1 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **171e** and **172e** that was separated by **HPLC** (156 mg, 88%) ($ds_{syn:syn}$ = 62 : 38, $ds_{syn:anti}$ = 93 : 7).

General procedure F: Synthesis of Bn-Protected *Anti* Glycolate Aldol Adducts

To a stirred solution of thiolpropionate ester **166** (150 mg, 0.256 mmol) in solvent (15 ml) at - 78 °C was added dicyclohexylboron chloride (166 μl, 0.770 mmol) then amine base (0.64 mmol). The reaction mixture was stirred at - 78 °C for 1 h, then benzaldehyde was added (82 μl, 0.77 mmol). The reaction was stirred at - 78 °C for 2 h and then at 0 °C for 1.5 h. The mixture was quenched by the addition of pH 7 buffer and methanol (1:1, 4 ml) and diluted with methanol (4 ml) to make a homogeneous solution. After careful addition of H_2O_2 (30% aq, 2 ml) the mixture was stirred at RT for 30 min.

NaCl (20 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The combined organics were washed with $NaHCO_3$ (10 ml, sat aq) and NaCl (10 ml, sat aq), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldol product. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **181e** and **182e**. Major *anti* diastereoisomer **181e** was separated by **HPLC**.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*S*)- 2-benzoxy-3-hydroxy-3-phenyl thiopropionate 181e



181e **182e**

77 : 23
71 : 29
77 : 23

Method A: General procedure F was followed with thiolpropionate ester **166** (150 mg, 0.256 mmol) in CH_2Cl_2 (15 ml) at - 78 °C, to which was added dicyclohexylboron chloride (166 µl, 0.770 mmol), then triethylamine (90 µl, 0.64 mmol). Benzaldehyde was added (82 µl, 0.77 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **181e** and **182e** (174 mg, 98%), (ds $_{anti\,:\,anti}$ = 77 : 23, by **^{1}H NMR** integration of diastereomeric mixture). Major diastereoisomer **181e** was separated by **HPLC** (ds $_{anti\,:\,syn}$ = 98 : 2).

(2*S*,3*S*)-Major *anti* diastereoisomer 181e: HPLC R_t (20% EtOAc in hexane, flow rate:10 ml/min) = 21 min; **R_f** (20% EtOAc in hexane) = 0.27; **$[\alpha]_D$** = - 50 (c 0.70, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 3501 (OH), 1683 (C=O), 1603 (Ar), 1495 (Ar), 1321 (SO_2N), 1152 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.45–6.98 (18H, m, Ar*H*), 6.83 (2H, s, Ar*H*), 6.70 (2H, d, *J* = 7.0 Hz, Ar*H*), 4.80 (1H, d, *J* = 16.3 Hz, CH_AH$_B$Ph), 4.77 (1H, d, *J* = 8.8 Hz, C*H*Ph), 4.72 (1H, dd, *J* = 6.4 & 3.8 Hz, C*H*OH), 4.46 (1H, d, *J* = 11.3 Hz, CH_CH$_D$Ph), 4.45 (1H, d, *J* = 16.3 Hz, CH$_A$$H_B$Ph), 4.19 (1H, d, *J* = 11.3 Hz, CH$_C$$H_D$Ph), 4.13 (1H, dq, *J* = 8.8 & 6.8 Hz, C*H*CH$_3$), 3.97 (1H, d, *J* = 6.4 Hz, C*H*COS), 2.78 (1H, d, *J* = 3.8 Hz, O*H*), 2.30 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 1.20 (3H, d, *J* = 6.8 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 199.56 (C), 142.21 (C), 140.35 (2 × C), 139.62 (C), 138.57 (C), 138.37 (C), 136.15 (C), 132.69 (C), 132.01 (2 × CH), 128.37 (2 × CH), 128.26 (6 × CH), 127.96 (6 × CH), 127.56 (2 × CH), 127.23 (CH), 127.03 (CH), 126.80 (2 × CH), 86.87 (CH), 74.63 (CH), 74.06 (CH_2), 56.15 (CH), 50.87 (CH), 47.45 (CH_2), 22.73 (2 × CH_3), 20.76 (CH_3), 17.33 (CH_3); ***m/z*** (FAB, 3-NOBA) 694 ([M+H]$^+$, 3.1%),

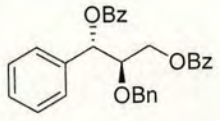
406 (37), 316 (100), 119 (100), 91 (100); **HRMS** (FAB, 3-NOBA) $[M]^+$ found 693.2585, $C_{41}H_{43}NO_5S_2$ requires 693.2583.

(2*R*,3*R*)-Minor *anti* diastereoisomer 182e: HPLC R_t (20% EtOAc in hexane, flow rate: 10 ml/min) = 22 min; R_f (20% EtOAc in hexane) = 0.26; **^{1}H NMR** δ (250 MHz, $CDCl_3$) diagnostic peaks 4.04 (1H, d, *J* = 6.1 Hz, C*H*COS), 2.89 (1H, d, *J* = 4.3 Hz, O*H*), 1.10 (3H, d, *J* = 6.8 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) diagnostic peaks 199.49 (C), 140.40 (2 × C), 139.88 (C), 138.65 (C), 138.29 (C), 136.22 (C), 128.58 (2 × CH), 128.22 (6 × CH), 127.91 (6 × CH), 127.52 (2 × CH), 127.13 (CH), 87.17 (CH), 74.81 (CH), 74.38 (CH_2), 56.38 (CH), 50.46 (CH), 47.25 (CH_2), 17.21 (CH_3).

Method B: General procedure F was followed with thiolpropionate ester **166** (150 mg, 0.256 mmol) in CH_2Cl_2 (15 ml) at - 78 °C, to which was added dicyclohexylboron chloride (166 µl, 0.770 mmol), then diisopropylethylamine (0.11 ml, 0.64 mmol). The reaction mixture was stirred at – 78 °C for 1 h, then benzaldehyde was added (82 µl, 0.77 mmol). The reaction was stirred at – 78 °C for 2 h and warmed to 0 °C for 2 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **181e** and **182e** (86 mg, 49%), (ds $_{anti\ :\ anti}$ = 71 : 29, by **^{1}H NMR** integration of diastereomeric mixture). Major diastereoisomer **181e** was separated by **HPLC** (ds $_{anti\ :\ syn}$ = 94 : 6).

Method C: General procedure F was followed with thiolpropionate ester **166** (150 mg, 0.256 mmol) in diethylether (15 ml) at - 78 °C, to which was added dicyclohexylboron chloride (166 µl, 0.770 mmol), then triethylamine (90 µl, 0.64 mmol). Benzaldehyde was added (82 µl, 0.77 mmol). Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of diastereoisomers **181e** and **182e** (163 mg, 92%), (ds $_{anti\ :\ anti}$ = 77 : 23, by **^{1}H NMR** integration of diastereomeric mixture). Major diastereoisomer **181e** was separated by **HPLC** (ds $_{anti\ :\ syn}$ = 99 : 1).

(1*S*,2*R*)-1,3-Dibenzoyl-2-benzyloxy-1-phenyl-propane 184[139]



To a solution of diol **183** (51 mg, 0.20 mmol) in pyridine (1.0 ml) at 0 °C was added DMAP (2.0 mg, 0.02 mmol) and benzoyl chloride (94 µl, 0.80 mmol). The reaction mixture was stirred at RT for 14 h. The reaction mixture was diluted with Et_2O (15 ml) and was washed with HCl (2 × 10 ml, 1 N aq), NaCl (1 × 10 ml), $NaHCO_3$ (2 × 10 ml, sat aq) and NaCl (2 × 10 ml, sat aq). The organics were dried ($MgSO_4$) and the volatiles removed under reduced pressure. Flash chromatography (10% EtOAc in hexane) afforded **184** as a colourless oil (88 mg, 96%); $\mathbf{R_f}$ (10% EtOAc in hexane) = 0.28; $[\alpha]_D$ = - 30.4 (c 2.50, benzene) lit.[139] - 31.6 (c 0.95, benzene); **^{1}H NMR** δ (250 MHz, $CDCl_3$)[139] 8.11 (2H, d, J = 7.1 Hz, ArH), 7.99 (2H, d, J = 7.1 Hz, ArH), 7.63-7.55 (2H, m, ArH), 7.50-7.30 (10H, m, ArH), 7.28-7.16 (4H, m, ArH), 6.31 (1H, d, J = 5.6 Hz, C*H*Ph), 4.68 (1H, d, J = 11.8 Hz, CH_AH$_B$Ph), 4.63 (1H, dd, J = 11.8 & 4.0 Hz, CH_2OBz), 4.61 (1H, d, J = 11.8 Hz, CH$_A$$H_B$Ph), 4.52 (1H, dd, J = 11.8 & 6.2 Hz, CH_2OBz), 4.24 (1H, ddd, J = 6.2, 5.6 & 4.0 Hz, C*H*OBn); **^{13}C NMR** δ (90.6 MHz, $CDCl_3$) 167.38 (C), 166.34 (C), 138.58 (C), 138.11 (C), 134.29 (CH), 134.11 (CH), 131.20 (C), 130.94 (C), 130.82 (2 × CH), 130.75 (2 × CH), 129.55 (2 × CH), 129.53 (2 × CH), 129.41 (5 × CH), 129.08 (2 × CH), 128.84 (CH), 128.26 (2 × CH), 79.85 (CH), 76.01 (CH), 73.93 (CH_2), 64.67 (CH_2).

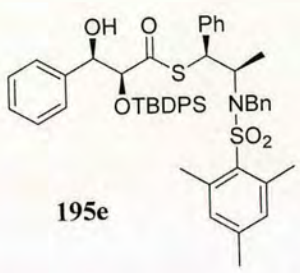
^{1}H spectroscopic data in good agreement with the literature.[139]

General procedure G: Synthesis of TBDPS-Protected *Syn* Glycolate Aldol Adducts

To a stirred solution of TBDPS-protected thiolester **190** (60 mg, 0.08 mmol) in CH_2Cl_2 (6 ml) at - 78 °C was added the boron chloride or triflate (0.24 mmol) then amine base (0.20 mmol). The reaction mixture was stirred at - 78 °C for 1 h, then benzaldehyde was added (26 µl, 0.24 mmol). The reaction was stirred at - 78 °C for 2 h and then at 0 °C for 1.5 h. The mixture was quenched by the addition of pH 7 buffer and methanol (1:1, 4 ml) and diluted with methanol (4 ml) to make a homogeneous solution. After careful addition of H_2O_2 (30% aq, 1 ml) the mixture was stirred at RT for 30 min.

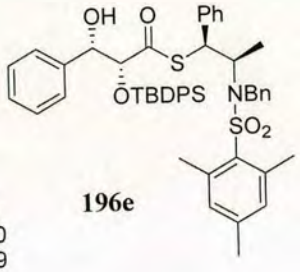
NaCl (10 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The combined organics were washed with $NaHCO_3$ (10 ml, sat aq) and NaCl (10 ml, sat aq), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldol product. Purification by flash chromatography (10% EtOAc in hexane) and then **HPLC** gave a mixture of diastereomeric aldol adducts **195e** and **196e**.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)- 2-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-3-phenyl thiolpropionate 195e



195e

92 : 8
90 : 10
61 : 39



196e

Method A: General procedure G was followed with TBDPS-protected thiolester **190** (60 mg, 0.08 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.24 ml, 0.24 mmol), triethylamine (28 µl, 0.20 mmol) and benzaldehyde (26 µl, 0.24 mmol). Purification by flash chromatography (10% EtOAc in hexane) and then **HPLC** gave a mixture of diastereoisomers **195e** and **196e** (56 mg, 82%), (ds $_{syn\ :\ syn}$ = 92 : 8, by **^{1}H NMR** integration of diastereomeric mixture).

(2*S*,3*R*)-Major *syn* diastereoisomer 195e: HPLC R_t (10% EtOAc in hexane, flow rate:10 ml/min) = 30 min; **R_f** (20% EtOAc in hexane) = 0.43; **$[\alpha]_D$** = + 24.4 (c 0.90, $CHCl_3$) (92:8 diastereomeric mixture); **ν_{max}** (neat)/cm^{-1} 3510 (OH), 1684 (C=O), 1600 (Ar), 1494 (Ar), 1321 (SO_2N), 1152 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.61-6.95 (21H, m, Ar*H*), 6.81 (2H, s, Ar*H*), 6.76 (2H, d, *J* = 7.0 Hz, Ar*H*), 6.62 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.75 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.59 (1H, d, *J* = 9.6 Hz, C*H*Ph), 4.56 (1H, d, *J* = 4.4 Hz, C*H*OH), 4.35 (1H, d, *J* = 4.4 Hz, C*H*COS), 4.33 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.10 (1H, dq, *J* = 6.8 Hz, C*H*CH_3), 2.30 (6H, s, 2 × *o*-CH_3), 2.24 (3H, s, *p*-CH_3), 1.11 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.07 (9H, s, C(CH_3)$_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 197.15 (C), 142.15 (C), 140.46 (2 × C), 139.82 (C), 138.32 (C), 137.72 (C), 135.78 (2 × CH), 135.73 (2 × CH), 132.66 (C), 132.21 (C), 132.01 (2 × CH), 131.72 (C), 130.13 (CH), 130.08 (CH), 128.67 (2 × CH), 128.21 (3 × CH), 128.13 (2 × CH), 127.80 (2 × CH), 127.75 (2 × CH), 127.62 (4 × CH), 127.23 (CH), 126.91 (CH), 126.41 (2 × CH), 82.49 (CH), 76.15 (CH), 55.93 (CH), 50.69 (CH), 47.24 (CH_2), 26.77 (3 × CH_3), 22.71 (2 × CH_3), 20.58 (CH_3), 19.13 (C), 17.93 (CH_3); ***m/z*** (ESI, –) 840 ([M–H]$^-$, 4%), 801 (95), 633 (18), 367 (100); **HRMS** (ESI, –) [M–H]$^-$ found 840.3186, $C_{50}H_{54}NO_5S_2Si$ requires 840.3207.

(2*R*,3*S*)-Minor *syn* diastereoisomer 196e: HPLC R_t (10% EtOAc in hexane, flow rate: 10 ml/min) = 30 min; R_f (20% EtOAc in hexane) = 0.43; **^{1}H NMR** δ (250 MHz, $CDCl_3$) diagnostic peaks 6.85 (2H, s, Ar*H*), 6.55 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.64 (1H, d, *J* = 9.7 Hz, C*H*Ph), 4.39 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.37 (1H, d, *J* = 3.9 Hz, C*H*COS), 1.12 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.04 (9H, s, C(CH_3)$_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) diagnostic peaks 196.70 (C), 142.12 (C), 140.40 (2 × C), 140.08 (C), 138.49 (C), 137.92 (C), 132.94 (C), 131.56 (C), 131.16 (C), 129.90 (CH), 128.99 (CH), 128.55 (2 × CH), 128.38 (CH), 128.30 (CH), 127.92 (2 × CH), 127.77 (2 × CH), 127.67 (4 × CH), 127.50 (2 × CH), 127.45 (2 × CH), 127.19 (CH), 126.85 (CH), 126.48 (2 × CH), 82.60 (CH), 76.27 (CH), 56.20 (CH), 50.51 (CH), 47.35 (CH_2), 22.48 (2 × CH_3), 20.79 (CH_3), 19.17 (C), 17.64 (CH_3).

Method B: General procedure G was followed with TBDPS-protected thiolester **190** (60 mg, 0.08 mmol), dicyclohexylboron chloride (52 μl, 0.24 mmol), triethylamine (28 μl, 0.20 mmol) and benzaldehyde (26 μl, 0.24 mmol). Purification by flash chromatography (10% EtOAc in hexane) and then **HPLC** gave a mixture of diastereoisomers **195e** and **196e** (65 mg, 95%), (ds $_{syn\ :\ syn}$ = 90 : 10, by **^{1}H NMR** integration of diastereomeric mixture).

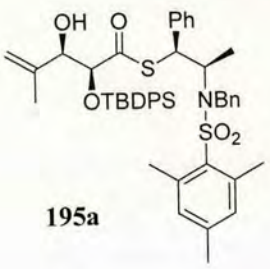
Method C: General procedure G was followed with TBDPS-protected thiolester **190** (60 mg, 0.08 mmol), dibutylboron triflate (1.0 M in hexane, 0.24 ml, 0.24 mmol), diisopropylethylamine (35 μl, 0.20 mmol) and benzaldehyde (26 μl, 0.24 mmol). Purification by flash chromatography (10% EtOAc in hexane) and then **HPLC** gave a mixture of diastereoisomers **195e** and **196e** (53 mg, 77%), (ds $_{syn\ :\ syn}$ = 61 : 39, by **^{1}H NMR** integration of diastereomeric mixture).

General procedure H: Optimised Synthesis of TBDPS-Protected *Syn* Glycolate Aldol Adducts

To a stirred solution of TBDPS-protected thiolester **190** (25 mg, 0.03 mmol) in CH_2Cl_2 (5 ml) at - 78 °C was added dicyclohexylboron triflate (1.0 M in hexane, 0.10 ml, 0.10 mmol) then triethylamine (14 μl, 0.10 mmol). The reaction mixture was stirred at - 78 °C for 1 h, then aldehyde was added (0.10 mmol). The reaction was stirred at - 78 °C for 2 h and then at 0 °C for 1.5 h. The mixture was quenched by the addition of pH 7 buffer and methanol (1:1, 4 ml) and diluted with methanol (4 ml) to make a homogeneous solution. After careful addition of H_2O_2 (30% aq, 1 ml) the mixture was stirred at RT for 30 min.

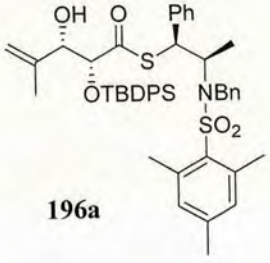
NaCl (10 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The combined organics were washed with $NaHCO_3$ (10 ml, sat aq) and NaCl (10 ml, sat aq), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldol product. Purification by flash chromatography (10% EtOAc in hexane) and then **HPLC** gave a mixture of diastereomeric aldol adducts.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)- 2-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-4-methyl-thiolpent-4-eneoate 195a



195a

92 : 8



196a

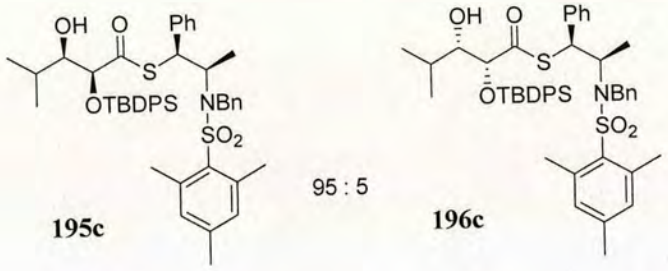
General procedure H was followed with TBDPS-protected thiolester **190** (25 mg, 0.03 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.10 ml, 0.10 mmol), triethylamine (14 µl, 0.10 mmol) and methacrolein (10 µl, 0.12 mmol). Purification by flash chromatography (10% EtOAc in hexane) and then **HPLC** gave a mixture of diastereoisomers **195a** and **196a** (21 mg, 76%), (ds *syn* : *syn* = 92 : 8, by **^{1}H NMR** integration of diastereomeric mixture).

(2*S*,3*R*)-Major *syn* diastereoisomer 195a: HPLC R_t (10% EtOAc in hexane, flow rate:10 ml/min) = 27 min; **R_f** (20% EtOAc in hexane) = 0.48; **$[\alpha]_D$** = - 4.0 (c 0.50, $CHCl_3$) (96:4 diastereomeric mixture); **ν_{max}** (neat)/cm^{-1} 3521 (OH), 1684 (C=O), 1603 (Ar), 1495 (Ar), 1321 (SO_2N), 1152 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.65-7.55 (4H, m, Ar*H*), 7.45-7.15 (11H, m, Ar*H*), 7.10 (1H, t, *J* = 7.7 Hz, Ar*H*), 6.98 (2H, t, *J* = 7.4 Hz, Ar*H*), 6.81 (2H, s, Ar*H*), 6.66 (2H, d, *J* = 7.8 Hz, Ar*H*), 4.81 (1H, d, *J* = 16.3 Hz, CH_AH$_B$Ph), 4.68 (1H, d, *J* = 9.4 Hz, C*H*Ph), 4.59 (1H, br s, =CH_CH$_D$), 4.53 (1H, br s, =CH$_C$$H_D$), 4.41 (1H, d, *J* = 16.3 Hz, CH$_A$$H_B$Ph), 4.29 (1H, d, *J* = 4.0 Hz, C*H*COS), 4.19 (1H, dq, *J* = 6.7 & 9.4 Hz, C*H*CH$_3$), 3.89 (1H, br s, C*H*OH), 2.29 (3H, s, *p*-CH_3), 2.27 (6H, s, 2 × *o*-CH_3), 2.08 (1H, br, O*H*), 1.25 (3H, s, CH$_2$=CCH_3), 1.20 (3H, d, *J* = 6.7 Hz, CHCH_3), 1.12 (9H, s, C(CH_3)$_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 196.87 (C), 142.19 (C), 140.68 (C), 140.47 (2 × C), 139.83 (C), 138.38 (C), 135.78 (2 × CH), 135.76 (2 × CH), 132.77 (C), 132.28 (C), 132.03 (2 × CH), 131.67 (C), 130.25 (CH), 130.16 (CH), 128.59 (2 × CH), 128.21 (2 × CH), 128.11 (2 × CH), 127.82 (2 × CH), 127.73 (2 × CH), 127.60 (2 × CH), 127.22 (CH), 126.93 (CH), 112.82 (CH_2), 80.17 (CH), 77.10 (CH), 56.07 (CH), 50.75 (CH), 47.39 (CH_2), 26.82 (3 × CH_3), 22.75 (2 × CH_3), 20.81 (CH_3), 19.21 (C), 18.48 (CH_3), 17.87 (CH_3); ***m/z*** (ESI, –) 804 ([M–H]$^-$,

100%), 415 (6); **HRMS** (ESI, –) $[M–H]^-$, found 804.3224, $C_{47}H_{54}NO_5S_2Si$ requires 804.3207.

(2*R*,3*S*)-Minor *syn* diastereoisomer 196a: HPLC R_t (10% EtOAc in hexane, flow rate: 10 ml/min) = 27 min; R_f (20% EtOAc in hexane) = 0.48; **^{1}H NMR** δ (250 MHz, $CDCl_3$) diagnostic peaks 6.79 (2H, s, Ar*H*), 6.44 (2H, d, *J* = 7.9 Hz, Ar*H*), 4.72 (1H, d, *J* = 8.6 Hz, C*H*Ph), 4.56 (1H, br s, $=CH_CH_D$), 4.49 (1H, br s, $=CH_CH_D$), 2.32 (3H, s, *p*-CH_3), 2.23 (6H, s, 2 × *o*-CH_3), 1.16 (3H, d, *J* = 7.0 Hz, $CHCH_3$), 1.06 (9H, s, $C(CH_3)_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) diagnostic peaks 140.39 (2 × C), 138.21 (C), 56.21 (CH), 22.88 (2 × CH_3).

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)- 2-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-4-methyl-thiolpentanoate 195c



195c **196c**

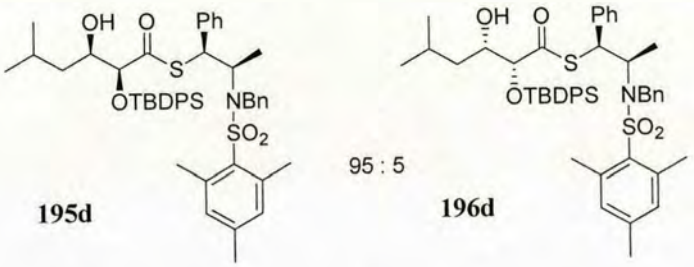
General procedure H was followed with TBDPS-protected thiolester **190** (25 mg, 0.03 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.10 ml, 0.10 mmol), triethylamine (14 µl, 0.10 mmol) and isobutyraldehyde (10 µl, 0.12 mmol). Purification by flash chromatography (10% EtOAc in hexane) and then **HPLC** gave a mixture of diastereoisomers **195c** and **196c** (20 mg, 73%), (ds $_{syn\ :\ syn}$ = 95 : 5, by **^{1}H NMR** integration of diastereomeric mixture).

(2*S*,3*R*)-Major *syn* diastereoisomer 195c: HPLC R_t (10% EtOAc in hexane, flow rate:10 ml/min) = 22 min; **R_f** (20% EtOAc in hexane) = 0.52; **$[\alpha]_D$** = - 10 (c 0.40, $CHCl_3$) (95:5 diastereomeric mixture); **ν_{max}** (neat)/cm^{-1} 3567 (OH), 1685 (C=O), 1603 (Ar), 1495 (Ar), 1322 (SO_2N), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.62-7.58 (4H, m, Ar*H*), 7.45-7.20 (11H, m, Ar*H*), 7.11 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.00 (2H, t, *J* = 7.8 Hz, Ar*H*), 6.81 (2H, s, Ar*H*), 6.70 (2H, d, *J* = 7.1 Hz, Ar*H*), 4.81 (1H, d, *J* = 16.3 Hz, CH_AH$_B$Ph), 4.71 (1H, d, *J* = 9.2 Hz, C*H*Ph), 4.43 (1H, d, *J* = 16.3 Hz, CH$_A$$H_B$Ph), 4.31 (1H, d, *J* = 3.5 Hz, C*H*COS), 4.22 (1H, dq, *J* = 6.8 & 9.2 Hz, C*H*CH$_3$), 3.03 (1H, dt, *J* = 7.8 & 3.8 Hz, C*H*OH), 2.28 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 1.80 (1H, d, *J* = 4.3 Hz, O*H*), 1.50-1.38 (1H, m, C*H*(CH$_3$)$_2$), 1.22 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.11 (9H, s, C(CH_3)$_3$), 0.61 (3H, d, *J* = 6.6 Hz, CHCH_3), 0.48 (3H, d, *J* = 6.6 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 198.34 (C), 142.21 (C), 140.45 (2 × C), 139.76 (C), 138.38 (C), 135.81 (2 × CH), 135.73 (2 × CH), 132.83 (C), 132.43 (C), 132.03 (2 × CH), 131.77 (C), 130.21 (CH), 130.14 (CH), 128.54 (2 × CH), 128.19 (4 × CH), 127.81 (2 × CH), 127.72 (2 × CH), 127.58 (2 × CH), 127.20 (CH), 126.94 (CH), 79.89 (CH), 79.67 (CH), 56.45 (CH), 50.70 (CH), 47.46 (CH_2), 28.74 (CH), 26.86 (3 × CH_3), 22.76 (2 × CH_3), 20.82 (CH_3), 19.24 (CH_3), 18.79 (CH_3), 18.33 (CH_3), 17.61 (C); ***m/z*** (ESI, –) 806

([M–H]$^-$, 100%), 367 (7); **HRMS** (ESI, –) [M–H]$^-$ found 806.3364, $C_{47}H_{56}NO_5S_2Si$ requires 806.3364.

(2*R*,3*S*)-Minor *syn* diastereoisomer 196c: HPLC R_t (10% EtOAc in hexane, flow rate: 10 ml/min) = 22 min; **R_f** (20% EtOAc in hexane) = 0.52; **^{1}H NMR** δ (250 MHz, $CDCl_3$) diagnostic peaks 0.71 (3H, d, J = 6.5 Hz, $CHCH_3$), 0.55 (3H, d, J = 6.9 Hz, $CHCH_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) diagnostic peaks 28.95 (CH).

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)- 2-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-5-methyl-thiolhexanoate 195d



195d **196d**

General procedure H was followed with TBDPS-protected thiolester **190** (25 mg, 0.03 mmol), dicyclohexylboron triflate (1.0 M in hexane, 0.10 ml, 0.10 mmol), triethylamine (14 µl, 0.10 mmol) and isovaleraldehyde (11 µl, 0.10 mmol). Purification by flash chromatography (10% EtOAc in hexane) and then **HPLC** gave a mixture of diastereoisomers **195d** and **196d** (18 mg, 64%), (ds $_{syn\ :\ syn}$ = 95 : 5, by **^{1}H NMR** integration of diastereomeric mixture).

(2*S*,3*R*)-Major *syn* diastereoisomer 195d: HPLC R_t (10% EtOAc in hexane, flow rate:10 ml/min) = 23 min; **R_f** (20% EtOAc in hexane) = 0.51; **$[\alpha]_D$** = - 8.0 (c 0.25, $CHCl_3$) (95:5 diastereomeric mixture); **ν_{max}** (neat)/cm^{-1} 3549 (OH), 1686 (C=O), 1603 (Ar), 1495 (Ar), 1323 (SO_2N), 1153 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.67-7.59 (4H, m, Ar*H*), 7.45-7.20 (11H, m, Ar*H*), 7.11 (1H, t, *J* = 7.6 Hz, Ar*H*), 7.00 (2H, t, *J* = 7.3 Hz, Ar*H*), 6.81 (2H, s, Ar*H*), 6.71 (2H, d, *J* = 7.8 Hz, Ar*H*), 4.81 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.70 (1H, d, *J* = 9.2 Hz, C*H*Ph), 4.41 (1H, d, *J* = 16.3 Hz, CH_AH_BPh), 4.25 (1H, d, *J* = 3.2 Hz, C*H*COS), 4.21 (1H, dq, *J* = 6.8 & 9.2 Hz, C*H*CH_3), 3.52-3.45 (1H, m, C*H*OH), 2.29 (9H, s, 2 × *o*-CH_3 & *p*-CH_3), 1.43 (1H, d, *J* = 5.9 Hz, O*H*) 1.42-1.39 (1H, m, C*H*$(CH_3)_2$), 1.21 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.13 (9H, s, C$(CH_3)_3$), 1.09 (1H, ddd, *J* = 13.8, 9.8 & 4.9 Hz, CH_CH$_D$), 0.75 (1H, ddd, *J* = 13.8, 9.2 & 3.3 Hz, CH$_C$$H_D$), 0.61 (3H, d, *J* = 6.5 Hz, CHCH_3), 0.49 (3H, d, *J* = 6.5 Hz, CHCH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 198.64 (C), 142.22 (C), 140.45 (2 × C), 139.85 (C), 138.37 (C), 135.84 (2 × CH), 135.67 (2 × CH), 132.82 (C), 132.75 (C), 132.03 (2 × CH), 131.76 (C), 130.20 (CH), 130.14 (CH), 128.51 (2 × CH), 128.22 (2 × CH), 128.15 (2 × CH), 127.86 (2 × CH), 127.74 (2 × CH), 127.61 (2 × CH), 127.22 (CH), 126.95 (CH), 82.28 (CH), 72.29 (CH), 56.19 (CH), 50.72 (CH), 47.49 (CH_2), 39.98 (CH_2), 26.91 (3 × CH_3),

23.92 (CH), 23.14 (CH_3), 22.75 (2 × CH_3), 21.18 (CH_3), 20.82 (CH_3), 19.34 (C), 17.77 (CH_3); ***m/z*** (ESI, –) 820 ($[M–H]^-$, 100%), 288 (4); **HRMS** (ESI, –) $[M–H]^-$ found 820.3540, $C_{48}H_{58}NO_5S_2Si$ requires 820.3520.

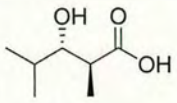
(2*R*,3*S*)-Minor *syn* diastereoisomer 196d: HPLC R_t (10% EtOAc in hexane, flow rate: 10 ml/min) = 23 min; **R_f** (20% EtOAc in hexane) = 0.51; **^{1}H NMR** δ (250 MHz, $CDCl_3$) diagnostic peaks 0.55 (3H, d, J = 6.5 Hz, $CHCH_3$).

6.4 EXPERIMENTAL PROCEDURES FOR CHAPTER 4

General procedure I: Hydrolysis Reaction

To a stirred solution of the unprotected aldol adduct (114 mg, 0.201 mmol) in THF (4 ml) was added a solution of LiOH (26 mg, 0.60 mmol) in H_2O (2 ml) at RT. After stirring at RT for 30 min, the mixture was acidified to pH 3 using HCl (1 N aq) and the solution was extracted with Et_2O (3 × 10 ml). The organics were washed with NaCl (2 × 10 ml, sat aq), and dried ($MgSO_4$), and the volatiles removed under reduced pressure to give a colourless oil which was purified by flash chromatography (20% EtOAc in hexane-1% AcOH) to recover the auxiliary **117** and the acid product as a colourless oil.

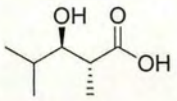
(2*S*,3*S*)-2,4-Dimethyl-3-hydroxy-pentanoic acid 143[97]



General procedure I was followed with aldol adduct **137c** (114 mg, 0.201 mmol) in THF (4 ml), to which was added a solution of LiOH (26 mg, 0.60 mmol) in H_2O (2 ml) at RT. Purification by flash chromatography (20% EtOAc in hexane-1% AcOH) gave auxiliary **117** (88 mg, 100%) and acid **143** as a colourless oil (29 mg, 99%); $\mathbf{R_f}$ (20% EtOAc in hexane-1% AcOH) = 0.23; $[\alpha]_D$ = + 14.3 (c 0.70, $CHCl_3$) lit.[97] + 14.1 (c 1.1, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3425 (br, OH), 1714 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 6.20 – 5.50 (2H, br, 2 × O*H*), 3.36 (1H, dd, *J* = 6.5 & 5.4 Hz, C*H*OH), 2.61 (1H, dq = qn, *J* = 7.1 Hz, C*H*CH_3), 1.80 – 1.67 (1H, sptd, *J* = 6.8 & 5.4 Hz, C*H*$(CH_3)_2$), 1.17 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 0.92 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3$)$_A$(CH_3)$_B$), 0.86 (3H, d, J = 6.8 Hz, CH(CH_3)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** δ (90.6 MHz, $CDCl_3$) 182.39 (C), 79.08 (CH), 43.70 (CH), 31.75 (CH), 20.77 (CH_3), 17.16 (CH_3), 15.62 (CH_3); **m/z** (THIOG) 147 ($[M+H]^+$, 60%), 129 (64), 45 (100); **HRMS** (THIOG) $[M+H]^+$ found 147.1024, $C_7H_{15}O_3$ requires 147.1021.

^{1}H spectroscopic data in good agreement with the literature.[97]

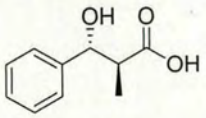
(2*R*,3*R*)-2,4-Dimethyl-3-hydroxy-pentanoic acid 144



General procedure I was followed with aldol adduct **138c** (114 mg, 0.201 mmol) in THF (4 ml), to which was added a solution of LiOH (26 mg, 0.60 mmol) in H_2O (2 ml) at RT. Purification by flash chromatography (20% EtOAc in hexane-1% AcOH) gave auxiliary **117** (78 mg, 88%) and acid **144** as a colourless oil (26 mg, 86%); $\mathbf{R_f}$ (20% EtOAc in hexane-1% AcOH) = 0.23; $[\alpha]_D$ = - 16.0 (c 0.25, $CHCl_3$)lit. [98] - 15.3 (c 1.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3417 (br, OH), 1713 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 5.35 – 4.45 (2H, br, 2 × O*H*), 3.36 (1H, t, *J* = 5.6 Hz, C*H*OH), 2.62 (1H, dq = qn, *J* = 7.1 Hz, C*H*CH_3), 1.80 – 1.67 (1H, m, C*H*$(CH_3)_2$), 1.18 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 0.92 (3H, d, *J* = 6.7 Hz, CH(C*H*$_3$)$_A$$(CH_3)_B$), 0.87 (3H, d, *J* = 6.7 Hz, CH$(CH_3)_A$(C*H*$_3$)$_B$); **^{13}C NMR** δ (90.6 MHz, $CDCl_3$) 182.40 (C), 79.09 (CH), 43.71 (CH), 31.74 (CH), 20.77 (CH_3), 17.16 (CH_3), 15.62 (CH_3); **m/z** (THIOG) 147 ($[M+H]^+$, 49%), 129 (57), 91 (100); **HRMS** (THIOG) $[M+H]^+$ found 147.1024, $C_7H_{15}O_3$ requires 147.1021.

^{1}H spectroscopic data in good agreement with the literature.[98]

(2*S*,3*R*)-3-Hydroxy-2-methyl-3-phenyl propionic acid 145[97]



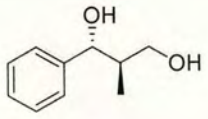
General procedure I was followed with aldol adduct **137e** (27 mg, 0.040 mmol) in THF (4 ml), to which was added a solution of LiOH (38 mg, 0.90 mmol) in H_2O (2 ml) at RT. Purification by flash chromatography (20% EtOAc in hexane-1% AcOH) gave auxiliary **117** (11 mg, 89%) and acid **145** as a colourless oil (8 mg, 98%); $\mathbf{R_f}$ (20% EtOAc in hexane-1% AcOH) = 0.16; $[\alpha]_D$ = + 17.5 (c 0.40, $CHCl_3$) lit.[97] + 17.8 (c 2.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3268 (br, OH), 1704 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.34 – 7.22 (5H, m, Ar*H*), 5.40-4.80 (2H, br, 2 × O*H*), 4.65 (1H, d, *J* = 8.9 Hz, C*H*OH), 2.78 (1H, dq, *J* = 8.9 & 7.2 Hz, C*H*CH_3), 0.95 (3H, d, *J* = 7.2 Hz, CHCH_3); **^{13}C NMR** δ (90.6 MHz, $CDCl_3$) 180.09 (C), 141.01 (C), 128.52 (2 × CH), 128.23 (CH), 126.65 (2 × CH), 77.10 (CH), 76.26 (CH), 14.24 (CH_3); **m/z** (THIOG) 181 ($[M+H]^+$, 14%), 163 (38), 91 (100); **HRMS** (THIOG) $[M+H]^+$ found 181.0870, $C_{10}H_{13}O_3$ requires 181.0865.

^{1}H spectroscopic data in good agreement with the literature.[97]

General procedure J: Reduction to Alcohol

To a solution of aldol adduct **137e** (100 mg, 0.166 mmol) in THF (2.5 ml) was added a solution of $NaBH_4$ (63 mg, 1.7 mmol) in THF (2.5 ml + 10 drops of H_2O) and the reaction stirred at RT for 1 h. HCl (1N aq) was added carefully until no more effervescence occurred and the solution extracted with CH_2Cl_2 (3 × 10 ml). The organics were washed with $NaHCO_3$ (1 × 10 ml) and H_2O (2 × 10 ml). The organics were combined, dried ($MgSO_4$) and the volatiles removed under reduced pressure. Flash chromatography (50% EtOAc in hexane) afforded the 1,3-diol product as a colourless oil and recovered auxiliary **117**.

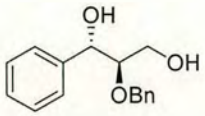
(1*R*,2*R*)-2-Methyl-1-phenyl-propane-1,3-diol 146[99]



General procedure J was followed with aldol adduct **137e** (100 mg, 0.166 mmol) in THF (2.5 ml), to which was added a solution of $NaBH_4$ (63 mg, 1.7 mmol) in THF (2.5 ml + 10 drops of H_2O). Purification by flash chromatography (50% EtOAc in hexane) afforded the 1,3-diol **146** as a colourless oil (46 mg, 99%) and recovered auxiliary **117** (23 mg, 83%); $\mathbf{R_f}$ (50% EtOAc in hexane) = 0.19; $[\alpha]_D$ = + 32.0 (c 0.50, $CHCl_3$), lit.[99] + 35.2 (c 0.34, $CHCl_3$); ν_{max} (neat) / cm^{-1} 3349 (br, 2 × OH), 1602 (Ar), 1495 (Ar); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.31-7.22 (5H, m, ArH), 4.47 (1H, d, J = 8.4 Hz, C*H*OH), 3.71 (1H, dd, J = 10.9 & 4.0 Hz, CH_AH_BOH), 3.66 (1H, dd, J = 10.9 & 7.1 Hz, CH_AH_BOH), 2.86-2.74 (2H, br, 2 × O*H*), 1.98 (1H, qnd, J = 7.0 & 4.0 Hz, C*H*CH_3), 0.63 (3H, d, J = 7.0 Hz, CH_3); **^{13}C NMR** δ (90.6 MHz, $CDCl_3$) 144.37 (C), 129.50 (2 × CH), 128.92 (CH), 127.70 (2 × CH), 81.94 (CH), 69.03 (CH_2), 42.73 (CH), 14.85 (CH_3); ***m/z*** (FAB, THIOG) 167 ($[M+H]^+$, 13%), 149 (66), 94 (100); **HRMS** (FAB, THIOG) $[M+H]^+$ found 167.1070, $C_{10}H_{15}O_2$ requires 167.1072.

^{1}H spectroscopic data in good agreement with the literature.[99]

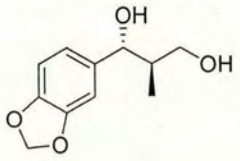
(1*S*,2*R*)-2-Benzyloxy-1-phenyl-propane-1,3-diol 183[139]



General procedure J was followed with aldol adduct **181e** (176 mg, 0.254 mmol) in THF (2.0 ml), to which was added a solution of $NaBH_4$ (98 mg, 2.5 mmol) in THF (2.0 ml + 15 drops of H_2O). Purification by flash chromatography (50% EtOAc in hexane) afforded the 1,3-diol **183** as a colourless oil (51 mg, 78%) and recovered auxiliary **117** (92 mg, 83%); $\mathbf{R_f}$ (50% EtOAc in hexane) = 0.24; **^{1}H NMR** δ (250 MHz, $CDCl_3$)[139] 7.65-7.35 (10H, m, ArH), 5.13 (1H, d, J = 5.3 Hz, C*H*OH), 4.72 (1H, d, J = 11.5 Hz, CH_AH$_B$Ph), 4.64 (1H, d, J = 11.5 Hz, CH$_A$$H_B$Ph), 3.90 (2H, br s, C$H_2$OH), 3.80 (1H, td, J = 5.1 & 3.9 Hz, C*H*OBn), 2.94 (1H, br, O*H*), 2.36 (1H, br, O*H*); **^{13}C NMR** δ (90.6 MHz, $CDCl_3$) 141.96 (C), 138.73 (C), 129.52 (2 × CH), 129.43 (2 × CH), 129.02 (2 × CH), 128.97 (CH), 128.80 (CH), 127.43 (2 × CH), 83.33 (CH), 75.19 (CH), 73.34 (CH_2), 62.47 (CH_2).

^{1}H spectroscopic data in good agreement with the literature.[139]

(1*R*,2*R*)-2-Methyl-1-piperonyl-propane-1,3-diol 201



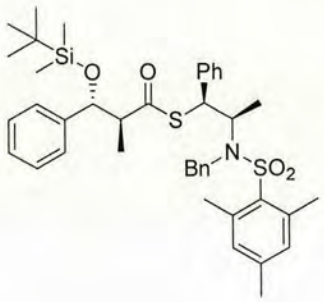
General procedure J was followed with aldol adduct **137f** (10 mg, 0.020 mmol) in THF (5 ml), to which was added a solution of $NaBH_4$ (38 mg, 1.0 mmol) in THF (5 ml + 20 drops of H_2O) and the reaction stirred at RT for 14 h. Purification by flash chromatography (50% EtOAc in hexane) afforded the 1,3-diol **201** as a colourless oil (3 mg, 94%) and recovered auxiliary **117** (6 mg, 88%); $\mathbf{R_f}$ (50% EtOAc in hexane) = 0.24; **^{1}H NMR** δ (250 MHz, $CDCl_3$) 6.80 (1H, s, Ar*H*), 6.71 (2H, d, J = 1.0 Hz, Ar*H*), 5.89 (2H, s, OCH_2O), 4.39 (1H, d, J = 8.6 Hz, C*H*OH), 3.72 (1H, dd, J = 10.9 & 3.8 Hz, CH_AH_BOH), 3.64 (1H, dd, J = 10.9 & 7.4 Hz, CH_AH_BOH), 2.02 – 1.86 (1H, m, C*H*CH_3), 0.62 (3H, d, J = 7.0 Hz, CH_3CH).

General procedure K: Silyl Protection of Aldol Adducts

To a stirred solution of unprotected aldol-adduct (80 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) at 0 °C was added 2,6-lutidine (48 µl, 0.40 mmol) and then *tert*-butyldimethylsilyl triflate (70 µl, 0.30 mmol). The reaction mixture was stirred at 0 °C for 2 h.

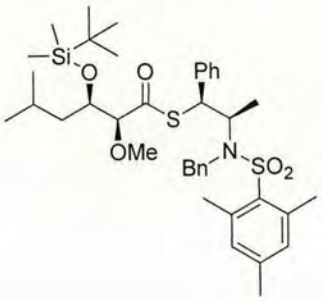
NaCl (20 ml, sat aq) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 ml). The combined organics were washed with NaCl (30 ml, sat aq), dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless oil. Purification by flash chromatography (20% EtOAc in hexane) gave the desired silyl protected aldol-adduct as a colourless oil.

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-(*tert*-butyl-dimethylsilyloxy)-2-methyl-3-phenylthiolpropionate 202



General procedure K was followed with aldol-adduct **137e** (80 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) at 0 °C, to which was added 2,6-lutidine (48 µl, 0.40 mmol) and then *tert*-butyldimethylsilyl triflate (70 µl, 0.30 mmol). The reaction mixture was stirred at 0 °C for 2 h. Purification by flash chromatography (20% EtOAc in hexane) gave a mixture of the desired product and the *tert*-butyldimethylsilyl alcohol that was separated by **HPLC** to give **202** (46 mg 48%, 88% brsm). **HPLC R_t** (15% EtOAc in hexane, flow rate: 10 ml/min) = 11 min; **R_f** (20% EtOAc in hexane) = 0.58; **$[\alpha]_D$** = + 103 (c 1.95, $CHCl_3$); **ν_{max}** (neat)/cm^{-1} 1692 (C=O), 1604 (Ar), 1495 (Ar), 1324 (SO_2N), 1155 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.58 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.47 - 7.20 (9H, m, Ar*H*), 7.08 (2H, t, *J* = 7.8 Hz, Ar*H*), 6.93 (2H, s, Ar*H*), 6.75 (2H, d, *J* = 7.0 Hz, Ar*H*), 4.94 (1H, d, *J* = 16.0 Hz, CH_AH$_B$Ph), 4.91 (1H, d, *J* = 10.0 Hz, C*H*Ph), 4.85 (1H, d, *J* = 8.8 Hz, C*H*OSi), 4.53 (1H, d, *J* = 16.0 Hz, CH$_A$*H*$_B$Ph), 4.25 (1H, dq, *J* = 10.0 & 6.8 Hz, C*H*CH$_3$), 2.90 (1H, dq, *J* = 8.8 & 7.1 Hz, C*H*CH$_3$), 2.42 (3H, s, *p*-C*H*$_3$), 2.37 (6H, s, 2 × *o*-C*H*$_3$), 1.43 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 0.85 (9H, s, 3 × C*H*$_3$), 0.75 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 0.00 (3H, s, C*H*$_3$), -0.23 (3H, s, C*H*$_3$); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 199.68 (C), 142.61 (C), 142.42 (C), 141.07 (2 × C), 140.73 (C), 138.91 (C), 133.20 (C), 132.53 (2 × CH), 129.39 (2 × CH), 128.85 (2 × CH), 128.68 (3 × CH), 128.51 (3 × CH), 128.17 (CH), 127.92 (2 × CH), 127.36 (2 × CH), 77.32 (CH), 57.88 (CH), 56.54 (CH), 51.55 (CH), 47.76 (CH_2), 26.14 (3 × CH_3), 23.25 (2 × CH_3), 21.31 (CH_3), 18.92 (CH_3), 18.38 (C), 15.07 (CH_3), -4.29 (CH_3), -4.80 (CH_3).

2'-(*N*-Benzyl-*N*-mesitylenesulfonylamino)-1'-phenylpropyl (1'*S*,2*S*,2'*R*,3*R*)-3-(*tert*-butyl-dimethylsilyloxy)-2-methoxy-5-methyl-thiolhexanoate 205



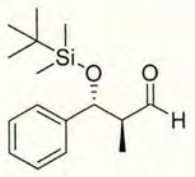
General procedure K was followed with aldol-adduct **167d** (56 mg, 0.090 mmol) in CH_2Cl_2 (1.5 ml) at 0 °C, to which was added 2,6-lutidine (32 µl, 0.27 mmol) and then *tert*-butyldimethylsilyl triflate (54 µl, 0.23 mmol). The reaction mixture was stirred at 0 °C for 2 h. Purification by flash chromatography (20% EtOAc in hexane) gave **205** (42 mg 63%, 90% brsm); $\mathbf{R_f}$ (20% EtOAc in hexane) = 0.64; $[\alpha]_D$ = - 12.1 (c 1.90, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1686 (C=O), 1603 (Ar), 1495 (Ar), 1155 (SO_2N); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.61 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.50 - 7.35 (3H, m, Ar*H*), 7.25 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.10 (2H, t, *J* = 7.7 Hz, Ar*H*), 6.95 (2H, s, Ar*H*), 6.80 (2H, d, *J* = 7.0 Hz, Ar*H*), 4.97 (1H, d, *J* = 16.2 Hz, CH_AH_BPh), 4.92 (1H, d, *J* = 9.5 Hz, C*H*Ph), 4.60 (1H, d, *J* = 16.2 Hz, CH$_A$*H*$_B$Ph), 4.30 (1H, dq, *J* = 9.5 & 6.8 Hz, C*H*CH_3), 3.86 (1H, m, C*H*OSi), 3.62 (1H, d, *J* = 4.9 Hz, C*H*OCH_3), 3.50 (3H, s, OCH_3), 2.45 (3H, s, *p*-CH_3), 2.40 (6H, s, 2 × *o*-CH_3), 1.70-1.55 (1H, m, C*H*$(CH_3)_2$), 1.45 (3H, d, *J* = 6.8 Hz, CHCH_3), 1.30-1.00 (2H, m, CH_2CH), 0.88 (3H, d, *J* = 6.5 Hz, CHCH_3), 0.87 (9H, s, 3 × CH_3), 0.78 (3H, d, *J* = 6.5 Hz, CHCH_3), 0.08 (3H, s, CH_3), 0.00 (3H, s, CH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 199.93 (C), 142.65 (C), 141.00 (2 × C), 140.31 (C), 138.96 (C), 133.17 (C), 132.53 (2 × CH), 129.22 (2 × CH), 128.80 (2 × CH), 128.69 (2 × CH), 128.12 (2 × CH), 127.81 (CH), 127.47 (CH), 91.48 (CH), 72.25 (CH), 59.95 (CH_3), 56.87 (CH), 50.65 (CH), 47.81 (CH_2), 42.34 (CH_2), 26.25 (3 × CH_3), 24.35 (CH), 23.38 (2 × CH_3), 23.24 (CH_3), 22.36 (CH_3), 21.30 (CH_3), 18.55 (C), 18.26 (CH_3), -3.97 (CH_3), -4.45 (CH_3).

General procedure L: Reduction to Aldehyde

To a stirred solution of TBS-protected aldol adduct (39 mg, 0.050 mmol) in CH_2Cl_2 (1 ml) at -78 °C was added DIBAL (solution 1 M in CH_2Cl_2, 100 µl, 0.100 mmol). The reaction mixture was stirred at -78 °C for 2 h and then quenched by addition of NH_4Cl (2 ml, sat aq), warmed to RT and stirred for a further 20 min.

The resulting mixture was filtered through Celite, dried over $MgSO_4$ and concentrated under reduced pressure to give a colourless oil which was purified by flash chromatography (10% EtOAc in hexane) to recover the auxiliary **117** and to isolate the TBS-protected aldehyde as a colourless oil.

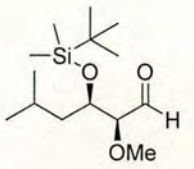
(2*S*,3*R*)-3-(*tert*-butyl-dimethylsilyloxy)-2-methyl-3-phenyl-propanal 203[150]



General procedure L was followed with TBS-protected aldol adduct **202** (39 mg, 0.050 mmol) in CH_2Cl_2 (1 ml) at -78 °C, to which was added DIBAL (solution 1 M in CH_2Cl_2, 100 µl, 0.100 mmol). Purification by flash chromatography (10% EtOAc in hexane) recovered auxiliary **117** (20 mg, 84%) and afforded TBS-protected aldehyde **203** as a colourless oil (2 mg, 13%); $\mathbf{R_f}$ (10% EtOAc in hexane) = 0.53; $[\alpha]_D$ = + 40.0 (c 0.10, $CHCl_3$), lit. ent.[148] – 60.0 (c 0.90, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2709 (CHO), 1727 (CHO), 1602 (Ar), 1492 (Ar); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 10.05 (1H, d, *J* = 2.7 Hz, C*H*O), 7.63 - 7.50 (5H, m, Ar*H*), 5.02 (1H, d, *J* = 7.6 Hz, C*H*OSi), 2.95 (1H, dqd, *J* = 7.6, 7.0 & 2.7 Hz, C*H*CH_3), 1.14 (3H, d, *J* = 7.0 Hz, CHC*H*$_3$), 1.10 (9H, s, 3 × C*H*$_3$), 0.25 (3H, s, C*H*$_3$Si), 0.00 (3H, s, C*H*$_3$Si); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 204.44 (C), 142.13 (C), 128.18 (2 × CH), 127.71 (CH), 126.58 (2 × CH), 76.69 (CH), 54.45 (CH), 25.57 (3 × CH_3), 17.94 (C), 10.97 (CH_3), -4.64 (CH_3), -5.34 (CH_3); ***m/z*** (FAB, THIOG) 279 ($[M+H]^+$, 6.5%), 237 (35), 221 (81), 163 (67), 116 (35), 108 (45), 94 (65).

^{1}H spectroscopic data in good agreement with the literature.[150]

(2*S*,3*R*)-3-(*tert*-butyl-dimethylsilanyloxy)-2-methoxy-5-methyl-hexanal 206

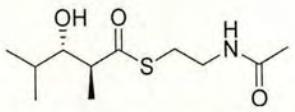


General procedure L was followed with TBS-protected aldol adduct **205** (39 mg, 0.05 mmol) in CH_2Cl_2 (1.5 ml) at -78 °C, to which was added DIBAL (solution 1 M in CH_2Cl_2, 220 µl, 0.220 mmol). Purification by flash chromatography (10% EtOAc in hexane) recovered auxiliary **117** (17 mg, 71%) and afforded TBS-protected aldehyde **206** as a colourless oil (8 mg, 53%); $\mathbf{R_f}$ (10% EtOAc in hexane) = 0.51; $[\alpha]_D$ = + 13 (c 0.15, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1734 (CHO); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 9.68 (1H, d, *J* = 1.5 Hz, CO*H*), 3.98 (1H, dt, *J* = 8.5 & 4.6 Hz, C*H*OSi), 3.49 (1H, dd, *J* = 4.6 & 1.5 Hz, C*H*OCH_3), 3.35 (3H, s, OCH_3), 1.65-1.50 (1H, m, C*H*$(CH_3)_2$), 1.40 (1H, ddd, *J* = 13.7, 8.1 & 4.9 Hz, CH_AH_BCH), 1.21 (1H, ddd, *J* = 13.7, 8.4 & 4.9 Hz, CH_AH_BCH), 0.82 (3H, d, *J* = 6.6 Hz, $CHCH_3$), 0.80 (3H, s, $CH(CH_3)_3$), 0.78 (3H, d, *J* = 6.6 Hz, $CHCH_3$), 0.01 (3H, s, CH_3), 0.00 (3H, s, CH_3); **^{13}C NMR** δ (90.5 MHz, $CDCl_3$) 204.90 (C), 89.24 (CH), 71.98 (CH), 59.82 (CH_3), 43.21 (CH_2), 26.83 (3 × CH_3), 25.10 (CH), 24.30 (CH_3), 23.07 (CH_3), 19.11 (C), -3.46 (CH_3), -3.52 (CH_3); ***m/z*** (ESI, +) 298 ($[M+Na]^+$, 100%), 196 (15), 205 (14); **HRMS** (ESI, +) $[M+Na]^+$ found 298.1927, $C_{14}H_{31}O_3NaSi$ requires 298.1935.

General procedure M: Transthiolesterification Reaction

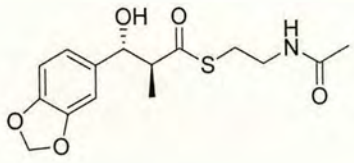
To a stirred solution of aldol adduct (100 mg, 0.176 mmol) in dry DMF (4 ml) at RT, was added diisopropylethylamine (460 µl, 2.64 mmol) followed by *N*-acetylcysteamine (290 µl, 2.73 mmol). The reaction mixture was stirred for 1 h at RT. NaCl (15 ml, sat aq) was added and the mixture was extracted with Et_2O (3 × 10 ml). The organics were washed with NaCl (2 × 10 ml, sat aq), and dried ($MgSO_4$), and the volatiles removed under reduced pressure to give a colourless oil which was purified by flash chromatography with gradient elution (20% EtOAc in hexane) to recover the auxiliary **117**, then (EtOAc to 10% MeOH in EtOAc) to isolate the SNAc thiolester product as a colourless oil.

2'-(Acetylamino)ethyl (2*S*,3*S*)-2,4-dimethyl-3-hydroxy-thiolpentanoate 209



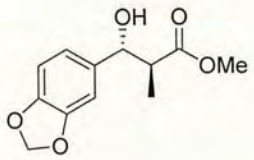
General procedure M was followed with aldol adduct **137c** (100 mg, 0.176 mmol) in dry DMF (4 ml) at RT, to which was added diisopropylethylamine (460 µl, 2.64 mmol) followed by *N*-acetylcysteamine (290 µl, 2.73 mmol). Purification by flash chromatography with gradient elution (20% EtOAc in hexane) recovered the auxiliary **117** (72 mg, 93%), then (EtOAc to 10% MeOH in EtOAc) gave the SNAc thiolester **209** as a colourless oil (39 mg, 88%); $\mathbf{R_f}$ (EtOAc) = 0.16; $[\alpha]_D$ = + 20.0 (c 0.25, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3399 (br, OH & NH), 1658 (C=O), 1555 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 5.90-5.60 (1H, br, N*H*), 3.42 – 3.36 (3H, m, C*H*OH & C*H*$_2$NHCO), 2.97 (2H, t, *J* = 6.1 Hz, C*H*$_2$S), 2.80 (1H, dq = qn, *J* = 7.0 Hz, C*H*CH$_3$), 2.30-2.15 (1H, br, O*H*), 1.89 (3H, s, C*H*$_3$CONH), 1.75 – 1.60 (1H, dspt ≡ oct, *J* = 6.8 Hz, C*H*(CH$_3$)$_2$), 1.15 (3H, d, *J* = 7.0 Hz, CHC*H*$_3$), 0.92 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3$)$_A$(CH$_3$)$_B$), 0.85 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_A$(C*H*$_3$)$_B$); **^{13}C NMR** δ (90.6 MHz, $CDCl_3$) 205.62 (C), 171.43 (C), 79.59 (CH), 52.60 (CH), 40.44 (CH_2), 31.80 (CH), 29.59 (CH_2), 24.22 (CH_3), 20.90 (CH_3), 16.96 (CH_3), 16.54 (CH_3); ***m/z*** (THIOG) 248 ($[M+H]^+$, 46%), 217 (32), 120 (59); **HRMS** (THIOG) $[M+H]^+$ found 248.1320, $C_{11}H_{22}NO_3S$ requires 248.1320.

2'-(Acetylamino)ethyl (2*S*,3*R*)-3-hydroxy-2-methyl-3-piperonyl thiolpropionate 210



General procedure M was followed with aldol adduct **137f** (90 mg, 0.14 mmol) in dry DMF (4 ml) at RT, to which was added diisopropylethylamine (360 µl, 2.09 mmol) followed by *N*-acetylcysteamine (230 µl, 2.09 mmol). Purification by flash chromatography with gradient elution (20% EtOAc in hexane) recovered the auxiliary **117** (47 mg, 77%), then (EtOAc to 10% MeOH in EtOAc) gave the SNAc thiolester **210** as a colourless oil (39 mg, 86%); $\mathbf{R_f}$ (EtOAc) = 0.20; $\mathbf{[\alpha]_D}$ = + 76 (c 0.55, $CHCl_3$); $\mathbf{\nu_{max}}$ (neat)/cm^{-1} 3307 (OH), 3085 (NH), 1652 (C=O), 1555 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 6.78 (1H, s, Ar*H*), 6.71 (2H, d, *J* = 1.0 Hz, Ar*H*), 5.88 (2H, s, OCH_2O), 5.87-5.81 (1H, br, N*H*), 4.65 (1H, d, *J* = 8.8 Hz, C*H*OH), 3.42-3.35 (2H, m, CH_2NHCO), 3.04-2.86 (3H, m, CH_2S & $CHCH_3$), 2.75-2.50 (1H, br, O*H*), 1.88 (3H, s, CH_3CONH), 0.91 (3H, d, *J* = 7.1 Hz, $CHCH_3$); **^{13}C NMR** δ (90.6 MHz, $CDCl_3$) 204.58 (C), 171.48 (C), 149.01 (C), 148.55 (C), 136.49 (C), 121.40 (CH), 109.14 (CH), 107.77 (CH), 102.19 (CH_2), 77.64 (CH), 56.84 (CH), 40.35 (CH_2), 29.77 (CH_2), 24.21 (CH_3), 16.33 (CH_3); ***m/z*** (THIOG) 326 ($[M+H]^+$, 15%), 308 (64), 217 (33), 189 (76), 91 (100); **HRMS** (THIOG) $[M+H]^+$ found 326.1060, $C_{15}H_{20}NO_5S$ requires 326.1062.

Methyl (2*S*,3*R*)-3-hydroxy-2-methyl-3-piperonylpropanoate 212



To a stirred solution of aldol adduct **137f** (26 mg, 0.040 mmol) in MeOH (2 ml) was added NaOMe (80 µl, 1 M in MeOH, 0.080 mmol) at RT. The reaction mixture was stirred at RT for 30 min. Cation exchange resin AG 50W-X8 in its hydrogen form was added, and the mixture stirred for 10 min until a neutral pH was reached. The reaction mixture was filtered to recover the resin and the filtrate was concentrated under reduced pressure to give a colourless oil which was purified by flash chromatography (20% EtOAc in Hexane) to recover the auxiliary **117** (18 mg, 100%) and the methyl ester **212** as a colourless oil (9.0 mg, 94%); $\mathbf{R_f}$ (20% EtOAc in Hexane) = 0.15; $[\alpha]_D$ = 23.3 (c 0.45, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3527 (OH), 1727 (C=O); **^{1}H NMR** δ (250 MHz, $CDCl_3$) 6.78 (1H, s, Ar*H*), 6.70 (2H, s, Ar*H*), 5.89 (2H, s, OCH_2), 4.60 (1H, dd, *J* = 8.7 & 3.9 Hz, C*H*OH), 3.67 (3H, s, OCH_3), 2.79 (1H, d, *J* = 3.9 Hz, O*H*), 2.68 (1H, dq, *J* = 8.7 & 7.2 Hz, C*H*CH_3), 0.93 (3H, d, *J* = 7.2 Hz, CH_3CH); **^{13}C NMR** δ (90.6 MHz, $CDCl_3$) 177.27 (C), 148.93 (C), 148.41 (C), 136.50 (C), 121.42 (CH), 109.10 (CH), 107.84 (CH), 102.12 (CH_2), 77.31 (CH), 52.99 (CH_3), 48.17 (CH), 15.49 (CH_3); ***m/z*** (FAB, THIOG) 237 ($[M-H]^+$, 66%), 221 (100), 214 (49), 197 (34), 165 (84); **HRMS** (FAB, THIOG) $[M-H]^+$ found 237.0684, $C_{12}H_{13}O_5$ requires 237.0685.

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ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Aq	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3,3,1]nonane
Bn	benzyl
Bp	boiling point
Brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
c-Hex	cyclohexyl
Cys	cysteine
DCC	*N,N*-dicyclohexylcarbodiimide
DCM	dichloromethane
DEPT	distortionless enhancement polarisation transfer
DIBAL	diisobutylaluminium hydride
DIC	*N,N*-diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DPM	diphenylmethyl
ds	diastereoselectivity
DSC	*N,N*-disuccinimidylcarbonate
EDCI	1-(3,3-dimethylaminopropyl)-3-ethyl-carbodiimide
EI	electron impact
Enant.	enantiomer
Eq	equivalents
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethylacetate
EtOH	ethanol
FAB	fast atom bombardment

HPLC	high perfomance liquid chromatography
HRMS	high resolution mass spectrum
HWE	Horner-Wadsworth-Emmons
Hz	hertz
^{i}Pr	isopropyl
IR	infra-red
L	unspecified ligand
LA	Lewis acid
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyl disilazide
Lit.	literature
Me	methyl
Mes	2,4,6-trimethylphenyl
MeCN	acetonitrile
MeOH	methanol
MOM	methoxymethyl
mp	melting point
MPAA	4-mercaptophenyl acetic acid
MPM	*p*-methoxyphenylmethyl
Ms	methanesulfonyl
NCL	native chemical ligation
NMR	nuclear magnetic resonance
OHA	1,2,3,4,6,7,8,9-octahydroanthracenyl
P	unspecified protecting group
PDC	pyridinium dichromate
c-Pen	dicyclopentyl
PMB	*p*-methoxybenzyl
Ph	phenyl
ppm	parts per million
Py	pyridine
R_f	retention factor
Rt	retention time
RT	room temperature
sat.	saturated

SEM	2-(trimethylsilyl)ethoxymethyl
SNAc	*N*-acetylcysteamine
TBDPS	*tert*-butyldiphenylsilyl
TBDMS	*tert*-butyldimethylsilyl
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
TES	triethylsilyl
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THIOG	1-thioglycine
TIP	2,4,6-triisopropylphenyl
TIPS	triisopropylsilyl
Tlc	thin layer chromatography
TMS	trimethylsilyl
Tol	4-methylphenyl
Tr	triphenylmethyl
Ts	*p*-toluenesulfonyl
UV	ultraviolet

APPENDIX 1: Crystal Structure Data of Glycolate Aldol Adduct **167e**

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A. CRYSTAL DATA

Empirical formula	C35 H39 N1 O5 S2
Formula weight	617.83
Wavelength	0.71073 A
Temperature	150 K
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 7.0937(3) A alpha = 90 deg. b = 13.3879(6) A beta = 90 deg. c = 33.7824(16) A gamma = 90 deg.
Volume	3208.3(2) A^3
Number of reflections for cell	0 (2 < theta < 31 deg.)
Z	4
Density (calculated)	1.279 Mg/m^3
Absorption coefficient	0.209 mm^-1
F(000)	1312

B. DATA COLLECTION

Crystal description	colourless block
Crystal size	0.55 x 0.35 x 0.23 mm
Instrument	Bruker SMART
Theta range for data collection	1.636 to 30.506 deg.
Index ranges	-9<=h<=9, -18<=k<=19, -47<=l<=43
Reflections collected	42448
Independent reflections	9221 [R(int) = 0.0393]
Scan type	\w
Absorption correction	Semi-empirical from equivalents (Tmin= 0.82, Tmax=0.95)

C. SOLUTION AND REFINEMENT.

Solution	direct (SIR92 (Altomare et al., 1994))
Refinement type	Full-matrix least-squares on F^2
Program used for refinement	CRYSTALS
Hydrogen atom placement	geom
Hydrogen atom treatment	constr
Data	9221
Restraints	24
Parameters	389
Goodness-of-fit on F^2	1.0405
Conventional R [F>4sigma(F)]	R1 = 0.0434 [7690 data]
Rw	0.0999
Absolute structure parameter	0.04(5)
Final maximum delta/sigma	0.001829
Weighting scheme	Sheldrick Weights
Largest diff. peak and hole	0.44 and -0.29 e.A^-3

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **167e**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	4256(1)	4648(1)	5860(1)	28
C(2)	3599(3)	3549(1)	5594(1)	26
O(3)	2000(2)	3276(1)	5546(1)	33
C(4)	5337(3)	2986(1)	5444(1)	30
C(5)	6224(3)	2342(1)	5773(1)	32
O(6)	7958(2)	1942(1)	5636(1)	47
C(7)	4976(3)	1486(1)	5901(1)	31
C(8)	5138(3)	557(1)	5722(1)	36
C(9)	4020(3)	-235(2)	5848(1)	42
C(10)	2729(4)	-104(2)	6145(1)	48
C(11)	2547(4)	825(2)	6323(1)	51
C(12)	3670(3)	1612(2)	6202(1)	43
O(13)	6748(2)	3681(1)	5330(1)	37
C(14)	6379(4)	4124(2)	4952(1)	47
C(15)	1983(2)	4950(1)	6087(1)	22
C(16)	1500(3)	4205(1)	6404(1)	27
C(17)	-62(3)	3588(1)	6357(1)	38
C(18)	-508(4)	2886(2)	6643(1)	53

C(19)	567(4)	2809(2)	6977(1)	57
C(20)	2107(4)	3420(2)	7029(1)	47
C(21)	2600(4)	4122(2)	6741(1)	42
C(22)	2044(2)	6041(1)	6242(1)	21
C(23)	2746(3)	6795(1)	5936(1)	27
N(24)	170(2)	6276(1)	6411(1)	22
C(25)	-1551(3)	6201(1)	6165(1)	29
C(26)	-1666(2)	6926(2)	5824(1)	29
C(27)	-1975(3)	6583(2)	5444(1)	41
C(28)	-2047(4)	7246(2)	5129(1)	55
C(29)	-1802(4)	8257(2)	5189(1)	50
C(30)	-1508(3)	8605(2)	5565(1)	42
C(31)	-1466(3)	7945(2)	5881(1)	36
S(32)	148(1)	7020(1)	6797(1)	24
O(33)	-1790(2)	7250(1)	6875(1)	34
O(34)	1397(2)	7846(1)	6731(1)	31
C(35)	1030(3)	6297(1)	7198(1)	23
C(36)	-147(3)	5539(1)	7354(1)	26
C(37)	421(3)	5068(1)	7700(1)	32
C(38)	2095(3)	5297(2)	7889(1)	35
C(39)	3247(3)	6015(2)	7721(1)	34
C(40)	2759(3)	6536(1)	7376(1)	27
C(41)	-1971(3)	5199(2)	7167(1)	32
C(42)	2643(4)	4782(2)	8270(1)	54
C(43)	4142(3)	7321(2)	7238(1)	37

Table 2. Bond lengths [A] and angles [deg] for **167e**.

S(1)-C(2)	1.7869(18)
S(1)-C(15)	1.8303(18)
C(2)-O(3)	1.202(2)
C(2)-C(4)	1.531(3)
C(4)-C(5)	1.540(3)
C(4)-O(13)	1.419(2)
C(4)-H(41)	0.984
C(5)-O(6)	1.419(2)
C(5)-C(7)	1.512(3)
C(5)-H(51)	0.990
O(6)-H(42)	0.833
C(7)-C(8)	1.387(3)
C(7)-C(12)	1.387(3)
C(8)-C(9)	1.390(3)
C(8)-H(81)	0.965
C(9)-C(10)	1.371(4)
C(9)-H(91)	0.952
C(10)-C(11)	1.387(3)
C(10)-H(101)	0.943
C(11)-C(12)	1.382(3)
C(11)-H(111)	0.942

C(12)-H(121)	0.946
O(13)-C(14)	1.433(3)
C(14)-H(141)	0.963
C(14)-H(142)	0.968
C(14)-H(143)	0.991
C(15)-C(16)	1.503(2)
C(15)-C(22)	1.553(2)
C(15)-H(151)	0.974
C(16)-C(17)	1.391(3)
C(16)-C(21)	1.384(3)
C(17)-C(18)	1.385(3)
C(17)-H(171)	0.972
C(18)-C(19)	1.365(4)
C(18)-H(181)	0.958
C(19)-C(20)	1.376(4)
C(19)-H(191)	0.948
C(20)-C(21)	1.399(3)
C(20)-H(201)	0.912
C(21)-H(211)	0.939
C(22)-C(23)	1.528(2)
C(22)-N(24)	1.480(2)
C(22)-H(221)	0.983
C(23)-H(231)	0.958
C(23)-H(232)	0.965
C(23)-H(233)	0.977

N(24)-C(25)	1.480(2)
N(24)-S(32)	1.6418(14)
C(25)-C(26)	1.509(3)
C(25)-H(251)	0.977
C(25)-H(252)	0.990
C(26)-C(27)	1.380(3)
C(26)-C(31)	1.384(3)
C(27)-C(28)	1.387(3)
C(27)-H(271)	0.951
C(28)-C(29)	1.380(4)
C(28)-H(281)	0.924
C(29)-C(30)	1.368(3)
C(29)-H(291)	0.940
C(30)-C(31)	1.388(3)
C(30)-H(301)	0.928
C(31)-H(311)	0.945
S(32)-O(33)	1.4325(14)
S(32)-O(34)	1.4346(14)
S(32)-C(35)	1.7783(18)
C(35)-C(36)	1.416(2)
C(35)-C(40)	1.404(3)
C(36)-C(37)	1.389(3)
C(36)-C(41)	1.509(3)
C(37)-C(38)	1.382(3)
C(37)-H(371)	0.939

C(38)-C(39)	1.384(3)
C(38)-C(42)	1.511(3)
C(39)-C(40)	1.400(3)
C(39)-H(391)	0.955
C(40)-C(43)	1.511(3)
C(41)-H(411)	0.966
C(41)-H(412)	0.958
C(41)-H(413)	0.954
C(42)-H(421)	0.943
C(42)-H(422)	0.941
C(42)-H(423)	0.953
C(43)-H(431)	0.974
C(43)-H(432)	0.964
C(43)-H(433)	0.976

C(2)-S(1)-C(15)	99.37(8)
S(1)-C(2)-O(3)	124.31(14)
S(1)-C(2)-C(4)	111.18(13)
O(3)-C(2)-C(4)	124.49(16)
C(2)-C(4)-C(5)	111.48(15)
C(2)-C(4)-O(13)	109.58(14)
C(5)-C(4)-O(13)	105.87(16)
C(2)-C(4)-H(41)	110.2
C(5)-C(4)-H(41)	109.8
O(13)-C(4)-H(41)	109.8

C(4)-C(5)-O(6)	109.28(16)
C(4)-C(5)-C(7)	113.05(16)
O(6)-C(5)-C(7)	108.35(15)
C(4)-C(5)-H(51)	108.1
O(6)-C(5)-H(51)	108.9
C(7)-C(5)-H(51)	109.1
C(5)-O(6)-H(42)	104.7
C(5)-C(7)-C(8)	120.50(19)
C(5)-C(7)-C(12)	120.61(17)
C(8)-C(7)-C(12)	118.88(19)
C(7)-C(8)-C(9)	120.3(2)
C(7)-C(8)-H(81)	118.4
C(9)-C(8)-H(81)	121.3
C(8)-C(9)-C(10)	120.5(2)
C(8)-C(9)-H(91)	118.7
C(10)-C(9)-H(91)	120.8
C(9)-C(10)-C(11)	119.6(2)
C(9)-C(10)-H(101)	119.7
C(11)-C(10)-H(101)	120.7
C(10)-C(11)-C(12)	120.2(2)
C(10)-C(11)-H(111)	120.3
C(12)-C(11)-H(111)	119.5
C(7)-C(12)-C(11)	120.6(2)
C(7)-C(12)-H(121)	118.9
C(11)-C(12)-H(121)	120.5

C(4)-O(13)-C(14)	112.56(17)
O(13)-C(14)-H(141)	106.6
O(13)-C(14)-H(142)	109.8
H(141)-C(14)-H(142)	109.3
O(13)-C(14)-H(143)	108.4
H(141)-C(14)-H(143)	111.3
H(142)-C(14)-H(143)	111.4
S(1)-C(15)-C(16)	110.68(12)
S(1)-C(15)-C(22)	108.93(11)
C(16)-C(15)-C(22)	112.96(14)
S(1)-C(15)-H(151)	107.0
C(16)-C(15)-H(151)	109.1
C(22)-C(15)-H(151)	108.0
C(15)-C(16)-C(17)	119.68(18)
C(15)-C(16)-C(21)	120.72(18)
C(17)-C(16)-C(21)	119.60(19)
C(16)-C(17)-C(18)	120.4(2)
C(16)-C(17)-H(171)	118.9
C(18)-C(17)-H(171)	120.6
C(17)-C(18)-C(19)	120.0(2)
C(17)-C(18)-H(181)	120.8
C(19)-C(18)-H(181)	119.3
C(18)-C(19)-C(20)	120.3(2)
C(18)-C(19)-H(191)	120.5
C(20)-C(19)-H(191)	119.2

C(19)-C(20)-C(21)	120.6(2)
C(19)-C(20)-H(201)	120.4
C(21)-C(20)-H(201)	119.0
C(20)-C(21)-C(16)	119.1(2)
C(20)-C(21)-H(211)	120.3
C(16)-C(21)-H(211)	120.6
C(15)-C(22)-C(23)	113.72(14)
C(15)-C(22)-N(24)	107.73(13)
C(23)-C(22)-N(24)	114.44(14)
C(15)-C(22)-H(221)	106.1
C(23)-C(22)-H(221)	106.5
N(24)-C(22)-H(221)	107.9
C(22)-C(23)-H(231)	108.2
C(22)-C(23)-H(232)	110.4
H(231)-C(23)-H(232)	109.3
C(22)-C(23)-H(233)	109.5
H(231)-C(23)-H(233)	108.7
H(232)-C(23)-H(233)	110.6
C(22)-N(24)-C(25)	120.66(14)
C(22)-N(24)-S(32)	116.36(11)
C(25)-N(24)-S(32)	118.61(12)
N(24)-C(25)-C(26)	115.43(15)
N(24)-C(25)-H(251)	106.7
C(26)-C(25)-H(251)	108.0
N(24)-C(25)-H(252)	107.7

C(26)-C(25)-H(252)	109.2
H(251)-C(25)-H(252)	109.7
C(25)-C(26)-C(27)	120.22(18)
C(25)-C(26)-C(31)	121.39(17)
C(27)-C(26)-C(31)	118.39(19)
C(26)-C(27)-C(28)	120.4(2)
C(26)-C(27)-H(271)	119.8
C(28)-C(27)-H(271)	119.8
C(27)-C(28)-C(29)	120.7(2)
C(27)-C(28)-H(281)	119.2
C(29)-C(28)-H(281)	120.1
C(28)-C(29)-C(30)	119.4(2)
C(28)-C(29)-H(291)	120.2
C(30)-C(29)-H(291)	120.5
C(29)-C(30)-C(31)	120.0(2)
C(29)-C(30)-H(301)	120.1
C(31)-C(30)-H(301)	119.8
C(30)-C(31)-C(26)	121.14(19)
C(30)-C(31)-H(311)	119.0
C(26)-C(31)-H(311)	119.9
N(24)-S(32)-O(33)	106.60(8)
N(24)-S(32)-O(34)	109.85(7)
O(33)-S(32)-O(34)	117.09(8)
N(24)-S(32)-C(35)	105.74(7)
O(33)-S(32)-C(35)	108.34(8)

O(34)-S(32)-C(35)	108.63(8)
S(32)-C(35)-C(36)	117.77(14)
S(32)-C(35)-C(40)	120.71(14)
C(36)-C(35)-C(40)	121.25(16)
C(35)-C(36)-C(37)	117.87(17)
C(35)-C(36)-C(41)	124.55(16)
C(37)-C(36)-C(41)	117.59(16)
C(36)-C(37)-C(38)	122.51(18)
C(36)-C(37)-H(371)	118.0
C(38)-C(37)-H(371)	119.5
C(37)-C(38)-C(39)	118.16(18)
C(37)-C(38)-C(42)	120.9(2)
C(39)-C(38)-C(42)	121.0(2)
C(38)-C(39)-C(40)	122.77(19)
C(38)-C(39)-H(391)	118.4
C(40)-C(39)-H(391)	118.8
C(35)-C(40)-C(39)	117.36(17)
C(35)-C(40)-C(43)	126.37(18)
C(39)-C(40)-C(43)	116.25(18)
C(36)-C(41)-H(411)	110.7
C(36)-C(41)-H(412)	110.6
H(411)-C(41)-H(412)	109.8
C(36)-C(41)-H(413)	108.1
H(411)-C(41)-H(413)	108.5
H(412)-C(41)-H(413)	109.0

C(38)-C(42)-H(421)	107.5
C(38)-C(42)-H(422)	108.4
H(421)-C(42)-H(422)	107.0
C(38)-C(42)-H(423)	112.8
H(421)-C(42)-H(423)	109.5
H(422)-C(42)-H(423)	111.4
C(40)-C(43)-H(431)	110.0
C(40)-C(43)-H(432)	110.3
H(431)-C(43)-H(432)	107.7
C(40)-C(43)-H(433)	111.6
H(431)-C(43)-H(433)	110.0
H(432)-C(43)-H(433)	107.1

Symmetry transformations used to generate equivalent atoms:

Table 3. Anisotropic displacement parameters (A^2 x 10^3) for **167e**.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(1)	27(1)	24(1)	34(1)	-9(1)	9(1)	-5(1)
C(2)	35(1)	20(1)	22(1)	0(1)	4(1)	-3(1)
O(3)	35(1)	28(1)	36(1)	-7(1)	-2(1)	-3(1)
C(4)	36(1)	23(1)	32(1)	-5(1)	8(1)	-3(1)
C(5)	29(1)	27(1)	40(1)	-5(1)	2(1)	2(1)
O(6)	36(1)	37(1)	66(1)	-6(1)	7(1)	5(1)
C(7)	33(1)	23(1)	37(1)	2(1)	-5(1)	4(1)
C(8)	42(1)	28(1)	36(1)	0(1)	-6(1)	5(1)
C(9)	56(1)	23(1)	47(1)	-1(1)	-14(1)	2(1)
C(10)	50(1)	29(1)	65(2)	12(1)	-6(1)	-6(1)
C(11)	54(2)	34(1)	66(2)	9(1)	18(1)	1(1)
C(12)	50(1)	24(1)	56(1)	3(1)	13(1)	6(1)
O(13)	41(1)	29(1)	41(1)	-5(1)	14(1)	-6(1)
C(14)	69(2)	35(1)	37(1)	-3(1)	22(1)	-10(1)
C(15)	23(1)	21(1)	23(1)	-1(1)	3(1)	-4(1)
C(16)	36(1)	19(1)	25(1)	2(1)	9(1)	3(1)
C(17)	42(1)	27(1)	45(1)	5(1)	13(1)	-4(1)
C(18)	61(2)	32(1)	66(2)	13(1)	26(1)	-3(1)

C(19)	89(2)	33(1)	49(1)	14(1)	31(1)	12(1)
C(20)	74(1)	37(1)	29(1)	2(1)	1(1)	21(1)
C(21)	68(1)	32(1)	26(1)	1(1)	1(1)	18(1)
C(22)	22(1)	21(1)	22(1)	0(1)	2(1)	-2(1)
C(23)	29(1)	23(1)	30(1)	2(1)	9(1)	-1(1)
N(24)	21(1)	24(1)	21(1)	0(1)	2(1)	0(1)
C(25)	22(1)	30(1)	34(1)	-2(1)	-2(1)	-3(1)
C(26)	21(1)	39(1)	29(1)	-2(1)	-3(1)	4(1)
C(27)	42(1)	48(1)	33(1)	-6(1)	-5(1)	-8(1)
C(28)	64(2)	72(2)	28(1)	0(1)	-13(1)	-11(1)
C(29)	57(1)	58(1)	33(1)	9(1)	-9(1)	0(1)
C(30)	49(1)	36(1)	40(1)	6(1)	-5(1)	11(1)
C(31)	48(1)	36(1)	25(1)	-2(1)	-2(1)	13(1)
S(32)	28(1)	20(1)	23(1)	0(1)	5(1)	2(1)
O(33)	32(1)	34(1)	34(1)	1(1)	6(1)	10(1)
O(34)	43(1)	22(1)	29(1)	-1(1)	3(1)	-3(1)
C(35)	28(1)	21(1)	19(1)	-2(1)	5(1)	1(1)
C(36)	31(1)	23(1)	24(1)	-4(1)	6(1)	1(1)
C(37)	48(1)	23(1)	25(1)	-1(1)	6(1)	-4(1)
C(38)	53(1)	25(1)	27(1)	-1(1)	-4(1)	3(1)
C(39)	40(1)	29(1)	33(1)	-6(1)	-6(1)	2(1)
C(40)	30(1)	24(1)	28(1)	-5(1)	4(1)	1(1)
C(41)	31(1)	31(1)	35(1)	2(1)	4(1)	-7(1)
C(42)	85(2)	41(1)	37(1)	10(1)	-18(1)	-5(1)
C(43)	29(1)	38(1)	44(1)	0(1)	1(1)	-7(1)

Table 4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **167e**.

	x	y	z	U(eq)
H(41)	5000	2562	5217	39
H(51)	6475	2778	6003	42
H(81)	6057	474	5515	46
H(91)	4171	-868	5724	53
H(101)	1969	-645	6226	61
H(111)	1652	926	6524	65
H(121)	3555	2247	6323	54
H(141)	7402	4578	4900	72
H(142)	6360	3612	4750	71
H(143)	5158	4481	4966	72
H(151)	1039	4915	5878	29
H(171)	-806	3640	6117	50
H(181)	-1570	2452	6611	68
H(191)	263	2335	7175	75
H(201)	2837	3363	7250	68
H(211)	3692	4511	6770	48
H(221)	2966	6046	6459	28
H(231)	2573	7452	6041	43

H(232)	2041	6732	5692	43
H(233)	4089	6688	5888	42
H(251)	-1573	5524	6056	36
H(252)	-2651	6300	6341	36
H(271)	-2134	5887	5398	52
H(281)	-2291	7004	4878	69
H(291)	-1821	8700	4973	61
H(301)	-1347	9284	5609	53
H(311)	-1278	8198	6139	45
H(371)	-371	4575	7807	41
H(391)	4430	6154	7843	44
H(411)	-2447	4610	7299	53
H(412)	-1797	5064	6891	52
H(413)	-2874	5722	7197	54
H(421)	3919	4935	8320	85
H(422)	2571	4088	8230	85
H(423)	1892	4988	8489	86
H(431)	5353	7226	7368	59
H(432)	4344	7265	6957	59
H(433)	3675	7995	7289	58
H(42)	8632	2440	5592	73

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Achieving High Selectivity and Facile Displacement with a New Thiol Auxiliary for Boron-Mediated Aldol Reactions

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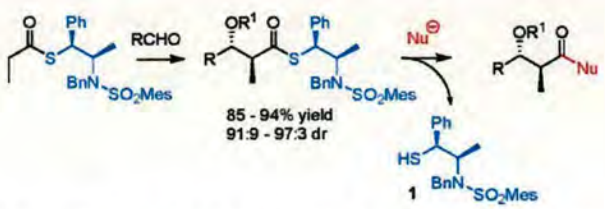
ABSTRACT



Synthesis of a new thiol auxiliary (1) is readily achieved (in five or six steps, >74% overall yield from norephedrine) and is shown to give high diastereoselectivity in boron-mediated *anti*-aldol reactions with a range of aldehydes. This new thiol auxiliary may be directly displaced by a range of nucleophiles under very mild conditions, to give the corresponding phosphonate esters, alcohols, acids, SNAC thiolesters, and methyl esters.

Despite recent advances in the catalytic aldol and organocatalytic aldol reactions,[1] auxiliary-controlled aldol reactions have maintained their place as one of the principle means through which the aldol reaction finds application in synthesis.[2] This is primarily due to the high yields and high diastereoselectivities which may be attained in auxiliary-controlled reactions and the facile separation of diastereomeric aldol adducts which allows the subsequent isolation of enantiopure species. Two auxiliaries currently have predominance in the field:[2] the Evans' oxazolidinone[3a−c] and its oxazolidinethione and thiazolidinethione counterparts for *syn*-aldol reactions and the Abiko−Masamune norephedrine-derived auxiliary for a range of *anti*-aldol reactions.[3d,e] However, for an auxiliary-based strategy to be truly useful, the auxiliary must be removable under a range of conditions.[4] Although this has clearly been demonstrated for the Evans' oxazolidinone, and to a lesser extent for the Abiko−Masamune auxiliary, there are still some nucleophilic displacement reactions which (though highly desirable synthetically) are unachieveable, or very low yielding, with either of these auxiliaries because of competitive retro-aldol or elimination reactions. In the course of synthetic studies directed toward the synthesis of the marine natural product octalactin A,[5] we have encountered these problems first hand.[6] Direct displacement by a phosphonate anion of the norephedrine-derived auxiliary in an *anti*-aldol adduct resulted in extensive decomposition of the aldol adduct through a retro-aldol mechanism, such that the acylated auxiliary was

(1) For recent reviews, see: (a) Sodeoka, M.; Hamashima, Y. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941−956. (b) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682−4698. (c) Kazmaier, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 2186−2188. (d) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719−724. (e) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570−579. (f) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858−860.

(2) (a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65−75. (b) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917−947.

(3) (a) Evans, D. A.; Bartroli, J. A.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77−91. (c) Evans, D. A.; Shaw, J. T. *Actual. Chim.* **2003**, 35−38. (d) Abiko, A.; Liu, J. F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586−2587. (e) Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387−395.

(4) For a recent review of auxiliary-mediated reactions, see: Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899−1930.

(5) Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 4682−4683.

(6) Hulme, A. N.; Howells, G. E. *Tetrahedron Lett.* **1997**, *38*, 8245−8248.

10.1021/ol0614774 CCC: $33.50
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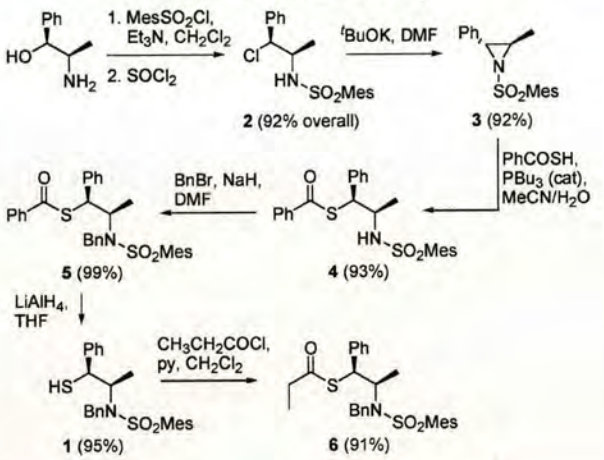
the major recovered product at the end of the reaction.[7] Following our earlier success in the achiral manifold with the use of thiolesters to address this displacement problem,[8] we therefore set out to develop a high-yielding route to a thiol alternative of the Abiko–Masamune auxiliary (Scheme 1).

Scheme 1. Synthesis of the Thiol Analogue of the Abiko–Masamune Auxiliary



(1*S*,2*R*)-(+)-Norephedrine was converted into its mesitylene sulfonamide,[3d,e] and subsequent treatment with thionyl chloride gave alkyl chloride **2** with net retention of stereochemistry.[9] The chloride was converted into aziridine **3**,[10] which was opened regio- and stereoselectively (>95:5) with thiolbenzoic acid in the presence of catalytic PBu_3.[11] Treatment of thiolbenzoate **4** with benzyl bromide and sodium hydride gave benzyl sulfonamide **5** exclusively.[12] Reduction of the benzoate using $LiAlH_4$ gave the thiol auxiliary **1** in excellent yield. Thiol **1** could also be accessed through saponification with NaOMe, thus avoiding the need for tedious purification from aluminum salts (five or six steps from norephedrine, >74% overall yield). The thiol was converted into its propionate derivative **6**, to allow the determination of the levels of diastereoselectivity that it could confer in a range of aldol reactions. The X-ray crystal structure of **6** has confirmed the overall net retention of stereochemistry of this synthetic sequence (Figure 1).

It has been reported by Abiko and Masamune that selective enolization may be achieved in the boron-mediated aldol

(7) Howells, G. E.; Hulme, A. N.; White, J. W. Unpublished results.
(8) Hulme, A. N.; Howells, G. E.; Walker, R. E. *Synlett* **1998**, 828–830.
(9) Flores-Parra, A.; Suarez-Moreno, P.; Sanchez-Ruiz, S. A.; Tlahuextl, M.; Jaen-Gaspar, J.; Tlahuext, H.; Salas-Coronado, R.; Cruz, A.; Noth, H.; Contreras, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1661–1672.
(10) On a small scale, direct conversion of the sulfonamido alcohol to aziridine **3** was achieved through in situ generation of the mesylate (MsCl, Et_3N, 87%).
(11) Fan, R.-H.; Hou, X.-L. *J. Org. Chem.* **2003**, *68*, 726–730.
(12) Significant levels of benzoate migration and concomitant thiol benzylation were observed when benzylation was attempted in the presence of other bases.

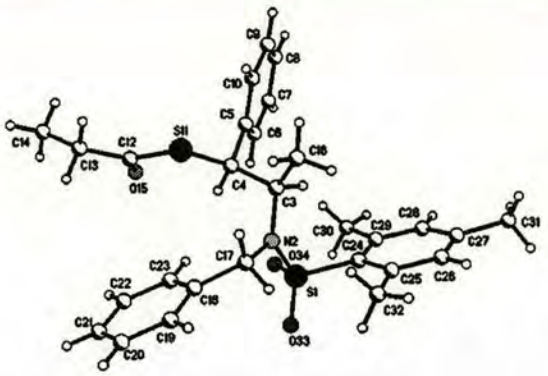
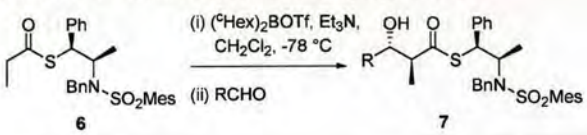
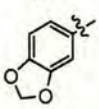


Figure 1. Crystal structure of thiopropionate **6**.

reaction of the norephedrine-derived auxiliary through the appropriate choice of reagents, thus leading to either *anti*- or *syn*-aldol adducts.[3d,e] With the classical oxygenated auxiliary, the formation of *anti*-aldol adducts is controlled by the presence of bulky ligands on the boron [(^{c}Hex)$_2$BOTf] and the addition of Et_3N at low temperatures to form the kinetic *E*(*O*)-enolate. We therefore set out by using these

Table 1. *anti*-Aldol Reaction of Thiopropionate **6**



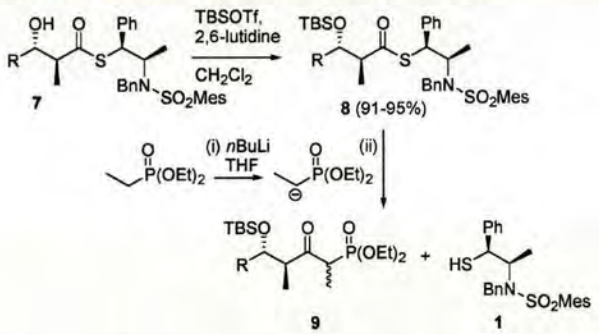
R	product	yield (%)[a] dr[b]	cf. Abiko-Masamune
	**7a**	92 (93:7)	79 (98:2)
	**7b**	90 (92:8)	97 (96:4)[13]
	**7c**	94 (92:8)	95 (98:2)[13]
	**7d**	94 (94:6)	--
	**7e**	85 (91:9)	93 (95:5)[13]
	**7f**	91 (97:3)	--

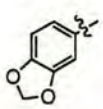
[a] Isolated yield of the major diastereomer. [b] Diastereomeric ratio determined by ^{1}H NMR integration.

optimized conditions with thiol auxiliary **1**. Gratifyingly, we found that we could obtain *anti*-aldol adducts with a range of aldehydes (vinyl, alkyl, and aromatic) in high yield and with high selectivity using the thiol auxiliary **1** (Table 1).[13] In all cases, our yields were comparable to that of the established Abiko−Masamune auxiliary, and only a minor erosion of diastereoselectivity was observed. As with the classic auxiliary, the minor diastereomer is thought to be the other anti diastereomer, rather than the syn diastereomer.[3d,e] This confirms the high selectivity of enolate formation in these reactions but suggests a minor erosion of facial selectivity of the resultant enolate in switching from the ester to the thiolester.

The main focus for the synthesis of the thiol auxiliary **1** was its potentially facile displacement with a range of nucleophiles. Of most immediate synthetic relevance to us was the displacement of the auxiliary by phosphonate nucleophiles (Table 2), which might then allow direct extension of the aldol adduct using a Horner−Wadsworth−Emmons (HWE) reaction.[14] Treatment of protected aldol adducts **8** with the lithium anion of diethyl ethane phosphonate was shown to give the desired phosphonate esters **9** in high yield (78−91%) and with varying diastereoselectivity

Table 2. Phosphonate Displacement of Auxiliary **1**

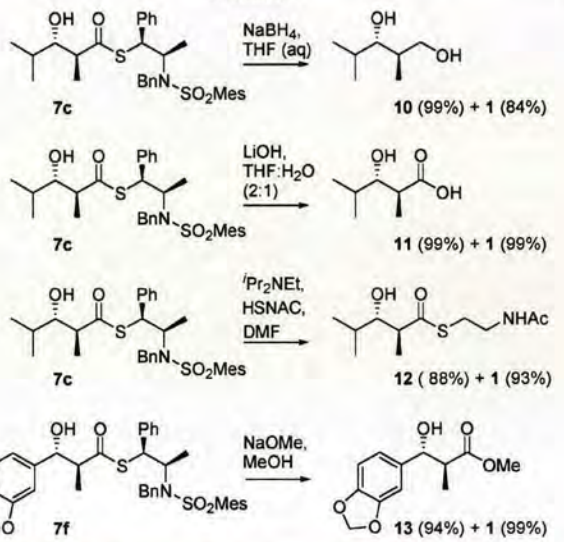


R	phosphonate	yield **9** (%)	yield **1** (%)
	**9a**	90	91
	**9b**	81	85
	**9c**	89	85
	**9d**	91	79
	**9f**	78	80

adjacent to the phosphonate (3:2 to 4:1 ratio of diastereomers). However, the diastereomeric phosphonate esters were not separated, as previous studies have shown that both give equal selectivity in the HWE reaction.[6] In all cases, the auxiliary **1** was also recovered in excellent yield (79−91%).

After the successful displacement of auxiliary **1** was achieved with a phosphonate anion, we decided to investigate the displacement reaction with other mild nucleophiles (Scheme 2). Initially, we examined reduction of the aldol

Scheme 2. Nucleophilic Displacement Reactions of *anti*-Aldol Adducts **7**



adducts to give the diol, a reaction which is typically achieved with rather harsh conditions ($LiAlH_4$, DIBALH) with the classic Abiko−Masamune auxiliary.[15] In contrast, we found that upon treatment of **7c** with $NaBH_4$ diol **10** was obtained in high yield in only 1 h (99%). We then decided to investigate the hydrolysis reactions of aldol adducts **7**, the counterparts of which have been shown to be quite sluggish with the classic auxiliary. LiOH-mediated hydrolysis of the thiolester **7c** was complete in only 30 min (as opposed to the typical 24−48 h reaction times required for hydrolysis of the Abiko−Masamune auxiliary)[16] and gave an excellent yield of the corresponding acid **11** (99%, Scheme 2).[17]

(13) Optimum conditions for aldol coupling with thiol auxiliary **1** were found to be: 3.0 equiv of Et_3N [cf. 2.4 equiv reported in ref 3e] and 2.0 equiv of $(^cHex)_2BOTf$ [cf. 2.0 equiv reported in ref 3e]. When conducting milligram scale reactions, an excess of aldehyde (3.0+ equiv) was used.

(14) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

(15) For recent synthetic examples, see: (a) Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223−226. (b) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215−4234. (c) Maleczka, R. E., Jr.; Terrell, L. R.; Geng, F.; Ward, J. S., III. *Org. Lett.* **2002**, *4*, 2841−2844. (d) Amarasinghe, K. K. D.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 9366−9367.

(16) For recent synthetic examples, see: (a) Kiho, T.; Nakayama, M.; Kogen, H. *Tetrahedron* **2003**, *59*, 1685−1697. (b) Andrus, M. B.; Meredith, E. L.; Simmons, B. L.; Sekhar, B. B. V. S.; Hicken, E. J. *Org. Lett.* **2002**, *4*, 3549−3552.

Similarly, transthiolesterification of **7c** was achieved under the extremely mild conditions reported by Raines et al. (*N*-acetylcysteamine, $^{i}Pr_2NEt$)[18] in only 1 h, to give an excellent yield of the SNAC thiolester **12** (88%). This latter procedure is notable because it avoids the need for a two-step hydrolysis/thiolesterification process which is typically used in the case of polyketide starter units derived from the Evans oxazolidinone.[19] [The use of trimethylaluminum in these transthiolesterification reactions as reported by Willis et al. (*N*-acetylcysteamine, Me_3Al, THF, 0 °C)[20] was not viable.[21]] Finally, transesterification of aldol adduct **7f** was very readily achieved by treatment with sodium methoxide, giving methyl ester **13** in 94% yield in only 30 min. In all of the successful displacement reactions, auxiliary **1** was recovered in high yield (84−99%).

In conclusion, we have developed an auxiliary which promotes highly selective *anti*-aldol adduct formation, while also offering facile displacement with a range of nucleophiles. The high yields associated with these reactions, relative ease of synthesis of the thiol auxiliary **1**, and its excellent bench stability make it an attractive alternative for use in synthesis.

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Supporting Information Available: Experimental procedures for the synthesis of thiol auxiliary **1**, for the synthesis of thiopropionate **6** and an *anti*-aldol reaction to give **7c**, and for the displacement reactions to give compounds **9c** and **10**−**13**. Spectroscopic data for compounds **7b** and **7e**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0614774

(17) If the hydrolysis reactions were left for extended time periods, partial degradation of the thiol auxiliary **1** was observed.

(18) Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2000**, *2*, 1939−1941.

(19) For recent examples of the two-step synthesis of SNAC thiolesters, see: (a) Wu, J.; Zaleski, T. J.; Valenzano, C.; Khosla, C.; Cane, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 17393−17404. (b) Aldrich, C. C.; Venkatraman, L.; Sherman, D. H.; Fecik, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 8910−8911. (c) Hartung, I. V.; Rude, M. A.; Schnarr, N. A.; Hunziker, D.; Khosla, C. *J. Am. Chem. Soc.* **2005**, *127*, 11202−11203.

(20) Le Sann, C.; Muñoz, D. M.; Saunders, N.; Simpson, T. J.; Smith, D. I.; Soulas, F.; Watts, P.; Willis, C. L. *Org. Biomol. Chem.* **2005**, *3*, 1719−1728.

(21) Complex mixtures were obtained under these conditions including the products of elimination and retroaldol reactions.